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(54) Title: PHENOL AND PYRIDINOL DERIVATIVES AS PHARMACEUTICALS

(57) Abstract

Fused aryl phenol/pyridinol derivatives are disclosed as medicaments.

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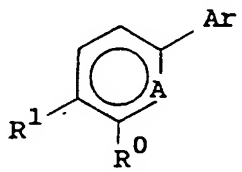
Phenol and Pyridinol derivatives as pharmaceuticals

The present invention relates to fused aryl derivatives, processes for their preparation, intermediates in their preparation, their use as medicaments and to pharmaceutical compositions comprising them.

The compounds of this invention are agonists of a cyclic AMP-dependent protein kinase (cA-PrK) (see J. Biol. Chem., 1989, 264, 8443 - 8446) and are of use in combatting such conditions where such agonism is thought to be beneficial. They are likely to have anti-proliferative, anti-aggregatory, cholesterol-lowering, smooth muscle relaxant, anti-allergic or anti-inflammatory activities. They are likely to be useful in the treatment of cancer, psoriasis, atheroschlerosis, thrombosis, chronic reversible lung disease such as asthma and bronchitis, allergic disease such as allergic asthma, allergic rhinitis and urticaria or gut motility disorders such as irritable bowel syndrome.

Accordingly the present invention provides compounds of the formula (1) :



(1)

or pharmaceutically acceptable salts thereof, wherein :

A is N or CH,

R^0 is OH or a bioprecursor thereof,
R^1 is A^0CO_2H, $P(X)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is a single bond, CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

X is O or S and

Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy, 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy, 3-phenanthryl, 9-phenanthryl, 2-quinolinyl, 4-quinolinyl, 3-thianaphthenyl or 2-benzofuranyl.

Bioprecursors of the groups R^0 and R^1 are derivatives thereof which are convertible <u>in vivo</u> into the groups R^0 and R^1.

A suitable bioprecursor of the group R^0 is OR^7 wherein R^7 is C_{1-4}alkanoyl (for example acetyl), arylC_{1-4}alkanoyl (for example phenyl C_{1-4}alkanoyl such as benzoyl), arylsulphonyl (for example optionally substituted phenylsulphonyl or toluenesulphonyl) or C_{1-4}alkylsulphonyl (for example methylsulphonyl). When A is N, R^7 can also be C_{1-4}alkyl, arylC_{1-4}alkyl (for

example phenylC_{1-4}-alkyl such as benzyl).

When R^1 is A^0CO_2H a suitable bioprecursor is $A^0CO_2R^8$ wherein R^8 is an ester-forming group.

When R^1 is $P(X)(OH)(OR^2)$ a suitable bioprecursor is $P(X)(OR^2)_2$ wherein X and R^2 are as hereinbefore defined or $P(X)(OR^2)(OR)$ wherein R is an O-protecting group. Suitable O-protecting groups include pivalolyloxymethyl, propionyloxymethyl and pivaloyloxycarbonyloxymethyl.

When R^1 is 5-tetrazolyl, a suitable bioprecursor is a N-protected derivative thereof. Suitable N-protecting groups include pivalolyloxymethyl, propionyloxymethyl and pivaloyloxycarbonyloxymethyl.

Alternatively bioprecursors of the groups R^0 and R^1 are those formed when R^1 and R^0 are linked together to form a cyclic structure such that R^1-R^0 is A^1CO_2 or A^2OCH_2O, in which :

A^1 is CH_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

A^2 is $P(X)OR^2$ or $CR^3(CO_2R^8)$, and

R^2 to R^6, R^8 and X are as hereinbefore defined.

Suitably R^0 is hydroxy or OR^7, preferably hydroxy.

Suitably R^1 is A^0CO_2H or $A^0CO_2R^8$.

Suitably R^1 is $P(X)(OH)(OR^2)$ or $P(X)(OR^2)_2$.

Suitably R^1 is SO_2H, SO_3H or 5-tetrazolyl.

Suitably R^1 and R^0 are linked together such that R^1-R^0 is A^1CO_2.

Suitably R^1 and R^0 are linked together such that R^1-R^0 is A^2OCH_2O.

By the term alkyl is meant both straight- and branched- chain alkyl.

Suitably R^2 is methyl, ethyl, propyl, butyl, pentyl, hexyl, 2-methoxyethyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclopropylmethyl.

Suitably R^3 is H, methyl or ethyl, preferably H or methyl.

Suitably R^4 is H, methyl, ethyl or propyl, preferably H or methyl.

Suitably R^5 and R^6 are independently methyl, ethyl or propyl, preferably together they form a 1,2-ethanediyl group.

Preferably X is O.

Suitably R^8 is C_{1-4}alkyl optionally substituted by hydroxy, e.g. 2-hydroxyethyl or arylC_{1-4}alkyl (for example phenylC_{1-4}alkyl such as benzyl).

Suitably Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy. Suitably Ar is 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy. Examples of C_{1-6}alkoxy include methoxy, ethoxy, propoxy, butoxy or pentyloxy.

Suitably Ar is 3-phenanthryl or 9-phenanthryl.

Suitably Ar is 2-quinolinyl or 4-quinolinyl.

Suitably Ar is 2-benzofuranyl or 3-thianaphthenyl.

Particular compounds of this invention include :

6-(2-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(1-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(2-benzofuranyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one,

6-(9-phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(3-phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(2-quinolinyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-[1-(4-methoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

3-carboxy-6-(2-naphthyl)pyridin-2(1H)-one,

3-carboxy-6-(1-naphthyl)pyridin-2(1H)-one,

ethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-butyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-hexyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

phenyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-butyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-hexyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl 2-hydroxy-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate,

2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-propionic acid,

2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

2-propoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphonic acid,

2-oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

ethyl 2-oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

7-aza-6-(1-naphthyl)benzofuran-2-one,

4-ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)-pyridine,

ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonothioate,

3-methoxycarbonyl-6-(2-naphthyl)pyridin-2(1H)-one,

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate,

3-(5-tetrazolyl)-6-[2-(1-propyloxy)naphthyl]pyridin-2(1H)-one,

6-[2-(1-pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

2-hydroxyethyl 2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylate,

2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxo-lane-2-carboxylic acid,

n-butyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

3-(5-tetrazolyl)-6-(3-thianaphthenyl)pyridin-2(1H)-one,

6-(4-quinolinyl)-3-(5-(tetrazolyl)pyridin-2(1H)-one,

6-[1-(4-hydroxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

2-methoxyethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

n-propyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-propyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

2-hydroxy-2-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

ethyl 2-methoxy-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2-ethoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

3-carboxy-6-(9-phenanthryl)pyridin-2(1H)-one,

6-[1-(4-propoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

ethyl 2-hydroxy-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2-oxo-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

2-hydroxy-2-[6(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

n-butyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphinic acid,

ethyl 2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

4-(1-naphthyl)salicylic acid,

ethyl 2-hydroxy-4-(1-naphthyl)phenyl phosphonate,

5-[2-hydroxy-4-(1-naphthyl)phenyl]tetrazole,

4-(2-naphthyl)salicylic acid,

ethyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate,

n-butyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate,

ethyl 2-hydroxy-4-(9-phenanthryl)phenyl phosphonate,

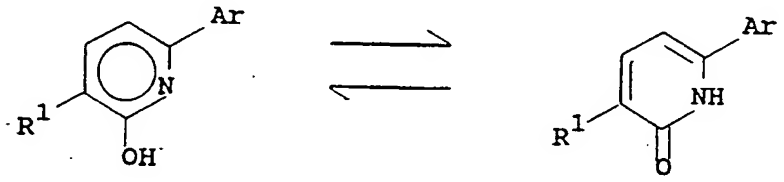
ethyl 4-(1-naphthyl)salicylate,

6-(1-naphthyl)-3-[5-(2-pivaloyloxymethyl)tetrazolyl]-pyridin-2(1H)-one, and

ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

and pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1). In particular when A is N and R^0 is hydroxy the compound can exist in its keto tautomeric form :



Compounds of the formulae (1) wherein R^1 is A^0CO_2H, $P(X)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or R^0 is hydroxy can form pharmaceutically acceptable base addition salts with metal ions, such as alkali metals for example sodium or potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, 2-pyrrolidone, cyclodextrin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The active ingredient may be administered as required for example from 1 - 8 times a day or by infusion. The compositions of the invention are agonists of a cA-PrK and are of use in combatting such conditions where such agonism is thought to be beneficial. Such conditions can

be treated by administration orally, sublingually topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1 - 5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a single pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H_1-antagonists, drugs used in the treatment of cancer such as those which inhibit the synthesis of or inactivate DNA, for example methotrexate, flouracil, cisplatin, actinomycin D, anti-atherschlerotic agents for example cholesterol lowering drugs such as HMGCoA reductase inhibitors, bile acid sequestrants, drugs for the treatment of psoriasis, for example retinoids, anthralin, anti-inflammatories for example cortiscosteroids, non-steroid anti-inflammatories such as aspirin, antithrombotics for example dipyridamole, or fibrinolytic agents.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which

process comprises :

a) for compounds wherein A is N and R^1 is CO_2H or CO_2R^8 in which R^8 is as hereinbefore defined,

reacting a compound of the formula (2) :

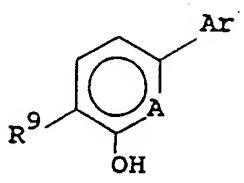
$$ArCOCH=CHY \qquad (2)$$

with a compound of the formula (3) :

$$R^8O_2CCH_2CONH_2 \qquad (3)$$

wherein Y is a displaceable group and Ar and R^8 are as hereinbefore defined and thereafter optionally converting CO_2R^8 into CO_2H; or

b) for compounds wherein R^1 is CO_2H, hydrolysing a compound of the formula (4) :



(4)

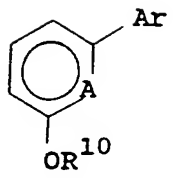
wherein A is N or CH and R^9 is cyano and Ar is as hereinbefore defined ; or

c) for compounds wherein R^1 is A^0CO_2H or $A^0CO_2R^8$ and :

i) A^0 is a single bond,

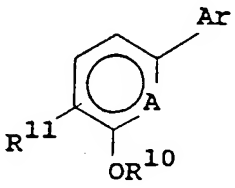
reacting in the presence of a strong base a compound of

the formula (5) :



(5)

wherein R^{10} is methyl and Ar and A are as hereinbefore defined with carbon dioxide to form a compound of the formula (6) :



(6)

wherein R^{11} is carboxy and Ar, A and R^{10} are as hereinbefore defined and thereafter optionally reacting with R^8OH wherein R^8 is as hereinbefore defined,

ii) A^0 is $CR^3(OR^4)$,

reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with a compound of the formula (7) :

$$R^3COCO_2R^8 \qquad (7)$$

wherein R^3 and R^8 are as hereinbefore defined to form a compound of the formula (6) wherein R^{11} is

$CR^3(OH)CO_2R^8$ and R^3, R^8, R^{10}, A and Ar are as hereinbefore defined and thereafter optionally reacting with a C_{1-3}alkylating agent to form the corresponding compound wherein R^{11} is $CR^3(OC_{1-3}alkyl)CO_2R^8$,

iii) A^0 is CO,

reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with a compound of the formula (8) :

$$R^8O_2CCO_2R^8 \qquad (8)$$

wherein R^8 is as hereinbefore defined to form a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined,

iv) A^0 is CH(OH),

reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a reducing agent to form the corresponding compound wherein R^{11} is $CH(OH)CO_2R^8$, or

v) A^0 is CH_2,

reacting a compound of the formula (6) wherein R^{11} is $COCO_2H$ or $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a suitable reducing agent to form the corresponding compound wherein R^{11} is CH_2CO_2H, or

vi) A^0 is $C(OR^5)(OR^6)$,

reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a C_{1-3}alcohol, 1,2-ethanediol or 1,3-propanediol to form the corresponding compound wherein R^{11} is $C(OR^5)(OR^6)CO_2R^8$,

vii) A^0 is CF_2,
reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CF_2CO_2R^8$, or

viii) A^0 is CHF,
reacting a compound of the formula (6) wherein R^{11} is $CH(OH)CO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CHFCO_2R^8$,

and thereafter optionally :

- converting the group OR^{10} into OH

- converting the group $A^0CO_2R^8$ into A^0CO_2H; or

d) for compounds wherein R^1 is CH_2CO_2H,
converting a compound of the formula (4) wherein R^9 is acetyl and Ar and A are as hereinbefore defined into the corresponding compound wherein R^9 is CH_2CO_2H; or

e) for compounds wherein R^1 is $P(O)(OH)(OR^2)$,
hydrolysing a compound of the formula (4) wherein R^9 is $P(O)(OR^2)_2$ and R^2, A and Ar are as hereinbefore defined; or

f) for compounds wherein R^1 is $P(S)(OH)(OR^2)$,
converting a compound of the formula (4) wherein R^9 is $P(O)(NHR^{12})(OR^2)$ and R^{12} is phenyl or C_{1-4}alkyl into the corresponding compound wherein R^9 is $P(S)(OH)(OR^2)$; or

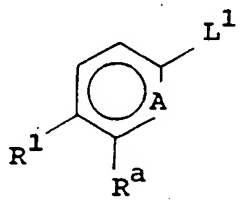
g) for compounds where R^1 is SO_3H,
reacting in the presence of a strong base a compound of

the formula (5) as hereinbefore defined with sulphuryl chloride or a chemical equivalent thereof and optionally converting the group OR^{10} into OH; or

h) for compounds wherein R^1 is SO_2H, reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with sulphur dioxide and optionally converting the group OR^{10} into OH; or

i) for compounds wherein R^1 is 5-tetrazolyl, reacting a compound of the formula (4) wherein R^9 is cyano or a compound of the formula (6) wherein R^{11} is cyano with an azide salt; or

j) for compounds wherein R^1 is as defined for compounds of the formula (1) reacting in the presence of a palladium catalyst a compound of the formula (9):



(9)

wherein R^1 and A are as hereinbefore defined and R^a is R^0 or OR^{10} as hereinbefore defined and L^1 is a leaving group with a compound of the formula (10):

$$ArB(OH)_2 \qquad (10)$$

wherein Ar is as hereinbefore defined and then, if necessary, converting the group OR^{10} into OH,

and optionally thereafter :

- forming a bioprecursor of R^0 and/or R^1
- forming a pharmaceutically acceptable salt.

Suitably Y in a compound of the formula (2) is hydroxy or a derivative thereof for example Y is protected hydroxy such as silyloxy, an acid residue (for example C_{1-6}alkanoyloxy) or an ether residue (for example methoxy or ethoxy). Alternatively Y is a secondary amino group, for example di-C_{1-6}alkylamino such as dimethylamino or a cyclic amino group such as piperidino, pyrrolidino or morpholino. Preferably Y is hydroxy or dimethylamino.

Suitably an alkali metal (e.g. sodium) salt of a compound of the formula (2) wherein Y is hydroxy is treated with a compound of the formula (3) under mildly alkaline aqueous conditions, for example in water in the presence of piperidine and glacial acetic acid, at an elevated temperature e.g. 30 - 200°C, preferably at the reflux temperature of the reaction mixture.

Alternatively a compound of the formula (2) wherein Y is a secondary amino group, for example dimethylamino, is treated with a compound of the formula (3) in a suitable solvent such as dimethylformamide, a C_{1-4}alkanol or pyridine at an elevated temperature e.g. 30 - 200°C, preferably at the reflux temperature of the reaction mixture optionally in the presence of a base such as pyridine or an alkali metal alkoxide, e.g. sodium methoxide.

Suitably the compound of the formula (1) wherein R^1 is CO_2R^8 can be hydrolysed to the corresponding

compound wherein R^1 is CO_2H in the presence of an aqueous acid or base, such as hydrochloric acid or sodium hydroxide.

A compound of the formula (4) wherein R^9 is cyano can suitably be hydrolysed to a compound of the formula (1) wherein R^1 is CO_2H by reaction with aqueous potassium hydroxide or with a mixture of acetic acid and aqueous hydrobromic acid at an elevated temperature, for example at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (5) is reacted with a strong base such as lithium diisopropylamide, or a C_{1-4}alkyl lithium in an organic solvent such as tetrahydrofuran, diethylether or dimethoxyethane with cooling (-100° - 0°C) to form the anion thereof. The strong base may be formed <u>in situ</u>, for example by the addition of a C_{1-4}alkyl lithium e.g. methyllithium followed by diisopropylamine.

The anion of a compound of the formula (5) is suitably reacted with carbon dioxide, a compound of the formula (7) or a compound of the formula (8) in an organic solvent such as tetrahydrofuran, diethylether or dimethoxyethane with cooling (-100° to 0°C) to form a compound of the formula (6) wherein R^{11} is carboxy, $CR^3(OH)CO_2R^8$ or $COCO_2R^8$ respectively. A suitable compound of the formula (7) is ethylpyruvate, or ethyl glyoxylate or a chemical equivalent thereof and a suitable compound of the formula (8) is diethyloxalate.

A compound of the formula (6) wherein R^{11} is $CR^3(OH)CO_2R^8$ is suitably reacted with a C_{1-3}alkylating agent such as iodomethane, iodopropane or dimethylsulphate in the presence of a base such as sodium hydride or potassium hydroxide in an organic solvent such as

dimethylformamide or dimethylsulphoxide at elevated (e.g. 30 - 80°C) or preferably ambient temperature to form the corresponding compound wherein R^{11} is $CR^3(OC_{1-3}$-alkyl)CO_2R^8. When potassium hydroxide is used as base the CO_2R^8 group may be directly converted to carboxy.

A compound of the formula (6) wherein R^{11} is $COCO_2R^8$ is suitably reacted with a reducing agent such as sodium borohydride, or diisobutylaluminium hydride in an organic solvent such as dichloromethane, a C_{1-4}alcohol e.g. ethanol, or acetic acid or mixtures thereof at ambient or elevated temperature (e.g. 30 - 80°C), or with cooling (e.g. 0 - 5°C) to form the corresponding compound wherein R^{11} is $CH(OH)CO_2R^8$.

A compound of the formula (6) wherein R^{11} is $COCO_2H$ or $COCO_2R^8$ is suitably reacted with a reducing agent such as a zinc amalgam in hydrochloric acid in the absence of a solvent or in a solvent such as ethanol, acetic acid or dioxan and hydrogen chloride gas at ambient or elevated temperature (e.g. 40-100°C) to form the corresponding compound wherein R^{11} is CH_2CO_2H. Under these reaction conditions the CO_2R^8 group is converted to carboxy.

A compound of the formula (6) wherein R^{11} is $COCO_2R^8$ is suitably reacted with a C_{1-3}alcohol, 1,2-ethanediol or 1,3-propanediol in the presence of an acid catalyst such as paratoluenesulphonic acid, concentrated sulphuric acid or anhydrous hydrogen chloride, at ambient or elevated temperature to form the corresponding compound wherein R^{11} is $C(OR^5)(OR^6)CO_2R^8$.

A compound of the formula (6) wherein R^{11} is $COCO_2R^8$ or $CHOHCO_2R^8$ is suitably reacted with a fluorinating

agent such as diethylaminosulphur trifluoride in an organic solvent such as a halohydrocarbon or an ether glyme, or THF at ambient or elevated temperature (e.g. 30-60°C) to form the corresponding compound where R^{11} is $CF_2CO_2R^8$ or $CHFCO_2R^8$ respectively.

A compound of the formula (6) wherein OR^{10} is methoxy can suitably be converted to the corresponding compound wherein OR^{10} is hydroxy by reaction with sodium iodide and chlorotrimethylsilane in an organic solvent such as acetonitrile, or a halohydrocarbon e.g. dichloromethane or chloroform at elevated (e.g. 30 - 80°C) or preferably ambient temperature. This method is particularly suitable for preparing compounds of the formula (1) wherein R^1 is $A^0CO_2R^8$ since the ester-forming group R^8 is not hydrolysed under the reaction conditions. Another method utilises sodium thiomethoxide in an organic solvent such as dimethyl-formamide at an elevated temperature for example 40 - 120°C. The more forcing conditions of this method are suitable for preparing compounds of formula (1) wherein R^1 is A^0CO_2H.

A compound of the formula (6) wherein R^{11} is $A^0CO_2R^8$ can suitably be converted to the corresponding compound wherein R^{11} is A^0CO_2H by reaction with an aqueous base such as sodium or potassium hydroxide at ambient or elevated temperature (e.g. 40 - 120°). This method is particularly suitable for preparing compounds of the formula (1) wherein R^0 is methoxy since the OR^{10} group is not hydrolysed. Another hydrolysis method utilises aqueous acid such as concentrated hydrochloric acid at an elevated temperature (e.g. 40 - 120°C) which provides directly compounds of the formula (1) wherein R^0 is hydroxy and R^1 is A^0CO_2H.

Suitably a compound of the formula (4) wherein R^9 is acetyl is converted to the corresponding compound where R^9 is CH_2CO_2H by reaction with sulphur and morpholine at elevated temperature 50 - 200°C, followed by hydrolysis with an aqueous base such as sodium hydroxide at elevated temperature, preferably at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (4) wherein R^9 is $P(O)(OR^2)_2$ is hydrolysed by reaction with an aqueous base such as sodium hydroxide optionally in a cosolvent such as a C_{1-4}alcohol at an elevated temperature (e.g. 40-100°C), preferably at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (4) wherein R^9 is $P(O)(NHR^{12})(OR^2)$ is converted to the corresponding compound wherein R^9 is $P(S)(OH)(OR^2)$ by reaction with a strong base such as sodium hydride in an organic solvent such as dimethoxyethane at ambient or elevated temperature, e.g. 40 - 100°C followed by reaction with carbon disulphide.

Suitably the anion of a compound of the formula (5) prepared as hereinbefore described is reacted with sulphuryl chloride or a chemical equivalent thereof or with sulphur dioxide in an organic solvent such as tetrahydrofuran with cooling (-100° - 0°C) to form after aqueous work-up a compound of the formula (6) wherein R^{11} is SO_3H or SO_2H respectively and OR^{10} is methoxy which if desired can be converted to the corresponding compound wherein OR^{10} is hydroxy as hereinbefore described.

A compound of the formula (4) wherein R^9 is cyano is suitably reacted with an azide salt such as ammonium,

sodium, potassium or aluminium azide in an organic solvent such as dimethylformamide, dimethylsulphoxide, N-methylpyrrolidinone or tetrahydrofuran at an elevated temperature e.g. 40 - 200°C, preferably at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (9) is reacted with a compound of the formula (10) in the presence of 1-50 mole %, preferably 2-10 mole %, of a palladium catalyst and a base such as triethylamine, sodium bicarbonate, or aqueous sodium carbonate and optionally lithium chloride in an organic solvent such as dimethylformamide, acetonitrile, toluene, tetrahydrofuran, ethanol, or mixtures thereof, at elevated temperature, (e.g. 30-150°C), preferably at the reflux temperature of the mixture. Suitably L^1 is halo for example iodo, bromo or chloro or trifluoromethylsulphonate. Subsequently the OR^{10} group can be converted to hydroxy as hereinbefore described for compounds of formula (6). Examples of palladium catalysts that can be used include:

tetrakis(triphenylphosphine)palladium ($Pd[PPh_3]_4$),
bis(triphenylphosphine)palladium dichloride ($Pd[PPh_3]_2Cl_2$),
[1,4-bis-(diphenylphosphine)butane]palladium dichloride ($Pd(dppb)Cl_2$),
[1,3-bis-(diphenylphosphine)propane]palladium dichloride ($Pd(dppp)Cl_2$),
[1,2-bis-(diphenylphosphine)ethane]palladium dichloride ($Pd(dppe)Cl_2$),
bis(tri-o-tolylphosphine)palladium diacetate or dichloride ($Pd(totp)(OAc)_2$ or $Pd(totp)Cl_2$), or
1,1'-bis(diphenylphosphine)ferrocinopalladium diacetate or dichloride ($Pd[dppf](OAc)_2$ or $Pd[dppf]Cl_2$).

If desired a compound of the formula (1) wherein R^1 is A^0CO_2H can be converted to the corresponding compound wherein R^1 is $A^0CO_2R^8$ by reaction with a compound R^8OH wherein R^8 is as hereinbefore defined.

A compound of the formula (1) wherein R^0 is OH can be converted to the corresponding compound where R^0 is OR^7 by reaction with R^7L^2 wherein R^7 is as hereinbefore defined and L^2 is a leaving group such as halo e.g. bromo, chloro, iodo.

If desired a compound of the formula (1) wherein R^1 is $P(X)(OR^2)(OH)$ can be converted to the corresponding compound wherein R^1 is $P(X)(OR^2)(OR)$ by reaction with a suitable O-protecting agent in standard manner. For example the compound can be reacted with a pivalolyloxymethyl halide.

A compound of the formula (1) wherein R^1 is 5-tetrazole can be reacted with a suitable N-protecting agent in standard manner, for example with a pivalolyloxymethyl halide.

A compound of the formula (1) wherein R^1-R^0 is A^1CO_2 is suitably prepared by heating a compound of the formula (1) wherein R^1 is A^1CO_2H and R^0 is OH with a dehydrating agent such as acetic anhydride, at an elevated temperature e.g. 40 - 200°C, preferably at the reflux temperature of the reaction mixture.

A compound of the formula (1) wherein R^1-R^0 is A^2OCH_2O is suitably prepared by reacting a compound of the formula (1) wherein R^1 is A^2OH and R^0 is OH with a dihalomethane such as diiodo- or dibromomethane in the presence of silver carbonate in an organic solvent such as

dimethylformamide at an elevated temperature e.g. 40 - 120°C.

Compounds of the formula (2) wherein Y is hydroxy can suitably be prepared by reaction under basic conditions of a compound of the formula (11) :

$$ArCOCH_3 \qquad (11)$$

wherein Ar is hereinbefore defined,

with a compound of the formula HCOL wherein L is a leaving group.

Suitably L is ethoxy or methoxy. Conveniently a solution of a compound of the formula (11) and a compound of the formula HCOL in a suitable organic solvent such as diethyl ether is treated with a suitable base such as an alkali metal alkoxide, e.g. sodium methoxide at ambient temperature. The resulting reaction mixture is preferably extracted with water and the aqueous extract which contains the alkali metal salt of a compound of the formula (2) wherein Y is hydroxy is then treated with a compound of the formula (3) as hereinbefore described.

Compounds of the formula (2) wherein Y is a secondary amino group (e.g. dimethylamino) can suitably be prepared by reacting a compound of the formula (11) with a compound of the formula $HC(OR^b)_2Y$ wherein R^b is C_{1-4}alkyl and Y is a secondary amino group (for example $HC(OR^b)_2Y$ is N,N-dimethylformamide dimethyl or diethyl acetal).

A compound of the formula (5) is suitably prepared by reacting a compound of the formula (4) wherein R^9 is hydrogen with an O-methylating agent such as dimethyl-

formamide dimethylacetal in dimethylformamide or trimethylphosphite at an elevated temperature e.g. 40 - 120°C or with iodomethane and silver carbonate in toluene or chloroform.

A compound of the formula (4) wherein A is N and R^9 is cyano, acetyl or hydrogen is suitably prepared by reaction of a compound of the formula (2) as hereinbefore defined with a compound of the formula (12) :

$$R^{13}CH_2CONH_2 \qquad (12)$$

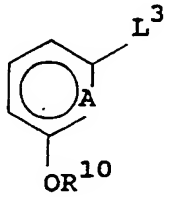
wherein R^{13} is cyano, acetyl or hydrogen respectively, in a similar manner to the reaction of compounds of formulae (2) and (3). Alternatively a compound of the formula (4) wherein R^9 is hydrogen can be prepared by reacting a compound of the formula (4) wherein R^9 is cyano with orthophosphoric acid at an elevated temperature, e.g. 50 - 200°C. A compound of the formula (4) wherein R^9 is acetyl can also be prepared by reacting a compound of the formula (4) wherein R^9 is cyano with methyl lithium followed by aqueous work up for example with aqueous ammonium chloride.

A compound of the formula (4) wherein A is N or CH and R^9 is cyano or acetyl and Ar is as hereinbefore defined can be suitably prepared by reaction of a compound of formula (6) wherein R^{11} is cyano or acetyl and Ar, A and R^{10} are as hereinbefore defined with a demethylating agent such as sodium iodide/chlorotrimethylsilane in the absence of solvent or in an organic solvent such as acetonitrile or chloroform at an elevated temperature (e.g. 40 to 100°C) or at ambient temperature.

A compound of formula (5) wherein A is CH and Ar is 1-naphthyl can be prepared by reaction of a compound of

formula (5) wherein Ar is 3,4-dihydro-1-naphthyl and A and R^{10} are as hereinbefore defined with an oxidising agent such as sulphur at elevated temperature e.g. 100-250°C in the absence of a solvent or in the presence of an organic solvent such as diglyme or triglyme.

A compound of formula (5) wherein Ar is 3,4-dihydro-1-naphthyl and A and R^{10} are as hereinbefore defined can be prepared by reacting the Grignard reagent, prepared from a compound of formula (13):



(13)

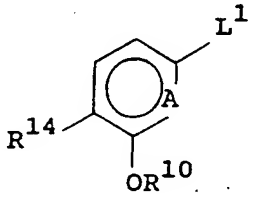
wherein L^3 is halo and A and R^{10} are as hereinbefore defined with 1-tetralone and dehydrating the product obtained, for example by heating with acetic anhydride.

Suitably L^3 is bromo or chloro and a compound of the formula (13) is reacted with magnesium in an organic solvent such as tetrahydrofuran or diethyl ether followed by 1-tetralone at ambient or elevated temperature, e.g. 40-100°C, preferably at the reflux temperature of the reaction mixture.

A compound of formula (5) is suitably prepared by treating in the presence of a palladium catalyst a compound of the formula (13) wherein L^3 is halo or trifluoromethylsulphonate and Ar and R^{10} are as hereinbefore defined with a compound of the formula (10) in an analogous manner to the reaction of the compounds of formulae (9) and (10).

A compound of formula (6) wherein R^{11} is cyano is suitably prepared by reacting the anion of a compound of formula (5) wherein Ar, A and R^{10} are as hereinbefore defined with dimethylformamide with cooling (e.g. -80 to 10°C), followed by ambient temperature and aqueous work-up. The resulting compound of formula (6) wherein R^{11} is carboxaldehyde is treated with hydroxylamine hydrochloride and sodium acetate in a suitable solvent such as ethanol or methanol at elevated temperature, e.g. 40-100°C, preferably at the reflux temperature of the reaction mixture followed by dehydrating the product obtained for example by heating with acetic anhydride.

A compound of the formula (6) wherein R^{11} is cyano or acetyl is suitably prepared by reacting in the presence of a palladium catalyst a compound of the formula (14):



(14)

wherein R^{14} is cyano or acetyl and R^{10} and L^1 are as hereinbefore defined, with a compound of formula (10) as hereinbefore defined, in analogous manner to the reaction of compounds of formulae (9) and (10).

A compound of the formula (4) wherein R^9 is $P(O)(OR^2)_2$ can be prepared by treating a compound of the formula (5) wherein R^{10} is $P(O)(OR^2)_2$ with a strong base such as lithium diisopropylamide in an organic solvent such as tetrahydrofuran with cooling (e.g. -100-0°C).

A compound of the formula (5) wherein R^{10} is $P(O)(OR^2)_2$ is suitably prepared by treating a compound of the formula (4) wherein R^9 is hydrogen with a compound of the formula (15):

$$ZP(O)(OR^2)_2 \qquad (15)$$

wherein Z is a leaving group and R^2 is as hereinbefore defined with a base such as diisopropylethylamine. Suitably Z is halo, for example chloro or bromo.

A compound of formula (5) wherein R^{10} is $P(O)(OR^2)_2$ can also be prepared by treating a compound of the formula (4) wherein R^9 is hydrogen with a compound of the formula (16):

$$HP(O)(OR^2)_2 \qquad (16)$$

wherein R^2 is as hereinbefore defined in the presence of an amine base such as triethylamine, and carbon tetrachloride.

Alternatively, a compound of the formula (4) wherein R^9 is $P(O)(OR^2)_2$ is suitably prepared by treating a compound of the formula (4) wherein R^9 is hydrogen with a compound of the formula (15) in the presence of a strong base such as lithium diisopropylamide in an organic solvent such as tetrahydrofuran with cooling (e.g. -100-0°C) without isolation of the intermediate compound of the formula (5) wherein R^{10} is $P(O)(OR^2)_2$.

A compound of formula (4) wherein R^9 is hydrogen is suitably prepared by demethylating a compound of formula (5) as hereinbefore defined. Suitably a compound of formula (5) is treated with boron tribromide in an organic solvent such as dichloromethane or toluene with cooling

(e.g. -80 to 10°C) followed by ambient temperature and aqueous work-up.

A compound of the formula (4) wherein R^9 is $P(O)(NHR^{12})(OR^2)$ can be prepared by reaction of a compound of the formula (4) wherein R^9 is $P(O)(OH)(OR^2)$ with carbon tetrachloride, triphenylphosphine and aniline or a C_{1-4}alkylamine in an organic solvent such as pyridine at ambient temperature or with cooling (e.g. -10 to 5°C). Alternatively a compound of the formula (4) where R^9 is $P(O)(OH)(OR^2)$ can be reacted with dimethylformamide and oxalyl chloride in an organic solvent such as a halohydrocarbon e.g. dichloromethane at ambient temperature, followed by reaction with aniline or a C_{1-4}alkylamine preferably with cooling (-10 to 5°C).

A compound of formula (10) is suitably prepared by reacting the organolithium or Grignard reagent, formed from a compound of formula (17):

$$Ar\text{-}L^4 \qquad (17)$$

wherein L^4 is bromo or iodo and Ar is as hereinbefore defined with a tri-C_{1-4}alkyl borate such as trimethyl, tri-isopropyl or tri-n-butyl borate in an organic solvent such as diethylether or tetrahydrofuran with cooling (e.g. -80 to 10°C).

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Cyclic-AMP Protein Kinase (cA-PrK) Agonist Activity

Type II cA-PrK was prepared from the cardiac muscle of a cow. The supernatant from a muscle homogenate (3 mls of 10 mM potassium phosphate, 1 mM EDTA per g tissue) was applied to a column of DEAE-cellulose equilibrated with the homogenisation buffer and the type II cA-PrK was eluted with homogenisation buffer containing 350 mM sodium chloride (Rannels et al., 1983, Methods Enzymol., 99, 55-62).

Type II cA-PrK was assayed for phosphotransferase activity by incubating the enzyme at 30°C for 5 minutes with [$-^{32}P$]-adenosine triphosphate and a suitable peptide substrate such as malantide (Malencik et al., 1983, Anal. Biochem., 132, 34-40). The reaction was terminated by the addition of hydrochloric acid and the [^{32}P]-phosphopeptide quantified by spotting the reaction mixture onto phosphocellulose papers. The concentration of compound required to give 10% phosphotransferase activation is given as the EC_{10} (μM). The compounds of Examples 1-32, 34-36, 38-46, 49-51, 53-54, 56, 58-61 and 63-65 had EC_{10} values in the range 0.04 - 100 μM.

Inhibition of Platelet Aggregation

Human platelet-rich-plasma was separated from freshly drawn blood (in acid/citrate/dextrose) and treated with 100 μM acetylsalicylic acid for 15 minutes at 37°C. A washed platelet suspension was then prepared in a Hepes-isotonic saline buffer after a single centrifugation step and adjusted to a concentration of $1.5x10^8$ cells/ml. Aliquots of this suspension were pre-incubated with compounds for 5 minutes at 37°C, then challenged with 1.0 μM U46619. The extent of aggregation after 2 minutes were expressed as a percentage of control and

results obtained are expressed as an IC_{50} (concentration to cause 50% inhibition of platelet aggregation, μM). The compounds of Examples 1-16, 20, 27-30, 33-36, 38-45, 51, 56, 59-61, 63-64 and 66 had IC_{50} values in the range 2-192 μM.

Anti-proliferative activity

Compounds under test were dissolved in dimethylsulphoxide and diluted 1:10,000 with DMEM (Dulbecco's Modified Eagle's Medium) containing 10% fetal bovine serum to give 12.5, 25, 50 and 100 μM concentrations used in the assay. Indicator cells consisting of 3 human colorectal cells lines (SW-620, SW-948 and HT-29) were plated at a cell density of 1000 cells in 0.1 ml of DMEM media in 96 well plates. Cells were incubated for 4 days at 37°C and 10% CO_2 atmosphere. On day 5, tetrazolium reagent (50 μg MTT/250 μl total medium volume) was added for 16 - 20 hours. Insoluble formazan was dissolved in 150 μl of dimethylsulphoxide and absorbance was measured using a microculture plate reader at 560 nm interfaced with an IBM computer. Cell line growth and inhibition were expressed in terms of mean absorbance unit of triplicate samples following subtraction of mean background absorbance. IC_{50} values (concentration that show 50% growth inhibition) were determined from the dose response curves. (Cancer Res., 48, 589-601, 1988). In the cell line SW-620 the compounds of Examples 4, 5, 28 and 61 had IC_{50} values in the range 17 - 82 μM. In the the cell line SW-948 the compounds of Examples 3, 4 and 28 had IC_{50} values in the range 18 - 46 μM. In the cell line HT-29 the compounds of Examples 4 and 5 had IC_{50} values of 95 and 31 μM respectively.

Inhibition of Spontaneous Contraction in Guinea-Pig Colon

Segments of isolated guinea-pig colon (2 cm) were suspended under 2 g tension in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. On-line computer capture and analysis was used to quantify the effects of test compounds on spontaneous contractions. Inhibitory responses were calculated as % maximum inhibition of spontaneous contraction distance over 3 consecutive pre and post dose 2 minute readings. The concentration of compound which caused 50% inhibition of the spontaneous contraction is given as the EC_{50} (μM). The compounds of Examples 1, 2, 4, 11, 12, 17, 20, 27-31, 35, 36, 42, 47, 51, 59-61, 63 and 64 had EC_{50} values in the range 1.5 - 210 μM.

Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methaneoepoxy-PGH_2) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of broncho-constriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The compounds of Examples 1, 2 and 14 reduced the U46619- induced bronchoconstriction in the range 10 - 35% when given at 10 μmole/kg.

Bronchodilatation - In vitro

Trachea were excised from guinea-pigs and, after removal of connective tissue, cut spirally into strips (0.8-1.2 cm). The strips were suspended under 1 g tension in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. The spirals were contracted by the addition of carbachol (final concentration, 1 μM) to the baths and a steady tension allowed to develop. Test compounds were then added in a cumulative manner to the bath and the experiment was terminated by the addition of sodium nitroprusside (final concentration, 100 μM). The relaxing effect of different concentrations of test compounds on carbachol induced sustained contraction was expressed as percentage of the relaxation obtained with sodium nitroprusside. The concentration of test compound which gave 50% relaxation is given as EC_{50}.

The compounds of Examples 7, 34, 35, 51, 58, 61 and 68 had EC_{50} values in the range 19 to 103 μM. The compounds of Examples 1, 2, 9, 11, 17, 29, 30, 42, 45, 58 and 64 at a concentration of 100 μM gave relaxation in the range 22 to 42%.

Example 1

6-(2-Naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) 2-Acetonaphthone (17 g) and dimethylformamide dimethylacetal (12.5 g) were combined in dimethylformamide (100 ml) and boiled for 24 hours. The deep red solution was cooled to room temperature, cyanoacetamide (8.4 g) and sodium methoxide (10.8 g) added and the mixture boiled for a further 90 minutes. After cooling to room temperature the reaction mixture was poured into water (300 ml) containing acetic acid (30 ml). The solid product formed was separated by filtration washed thoroughly with water and recrystallised from ethanol to give 3-cyano-6-(2-naphthyl)pyridin-2(1H)-one (12.6 g) m.p. 290-292°C.

(b) 3-Cyano-6-(2-naphthyl)pyridin-2(1H)-one (0.98 g) sodium azide (0.29 g) and ammonium chloride (0.23 g) in dimethylformamide were warmed to 120°C for 18 hours cooled to room temperature and poured into water (150 ml) containing acetic acid (5 ml). The resulting solid was separated by filtration, washed thoroughly with water and recrystallised from dimethylformamide/ethanol to give the title compound (0.51 g) m.p. 298-301°C.

Dimethylformamide can be replaced with advantage by N-methylpyrrolidin-2-one.

Example 2

6-(1-Naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 1-acetonaphthone (17 g), 3-cyano-6-(1-naphthyl)-pyridin-2(1H)-one (7.11 g) m.p. 264-266°C after

recrystallisation from ethanol, was prepared according to the method of Example 1(a).

(b) From 3-cyano-6-(1-naphthyl)pyridin-2(1H)-one (3.69 g), the title compound (0.9 g) m.p. 288-289°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b).

Example 3

6-(2-Benzofuranyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one

(a) From 2-acetylbenzofuran (8 g), 6-(2-benzofuranyl)-3-cyanopyridin-2(1H)-one (3.36 g) m.p. >330°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(a); δ(DMSO-d_6) 7.02(d,1H), 7.39(t,1H), 7.48(t,1H), 7.69(d,1H), 7.80(d,1H), 7.98(s,1H) and 8.23(d,1H).

(b) From 6-(2-benzofuranyl)-3-cyano-pyridin-2(1H)-one (2.36 g), the title compound (1.34 g) m.p. 248-250°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(b); δ(DMSO-d_6), 7.17(d,1H), 7.28-7.53(m,2H), 7.72(d,1H), 7.81(d,1H), 7.98(s,1H) and 8.53(d,1H).

Example 4

6-(9-Phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 9-acetylphenanthrene (29.74 g), 3-cyano-6-(9-phenanthryl)pyridin-2(1H)-one (31.93 g) m.p. 305-306°C after recrystallisation from dimethylformamide, was prepared according to the method of Example 1(a).

(b) From 3-cyano-6-(9-phenanthryl)pyridin-2(1H)-one (1 g), the title compound (0.67 g) m.p. 298°C after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(b); δ(DMSO-d_6), 6.78(d,1H), 7.69-7.88(m,4H), 7.93(d,1H), 8.06-8.17(m,2H), 8.59(d,1H), 8.92(d,1H) and 8.99(d,1H).

Example 5

6-(3-Phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 3-acetylphenanthrene (25 g), 3-cyano-6-(3-phenanthryl)pyridin-2(1H)-one (18.6 g) m.p. 240°C (decomp) after recrystallisation from dimethylformamide/water, was prepared according to the method of Example 1(a); δ(DMSO-d_6) 7.08(d,1H), 7.68-8.15(m,7H), 8.27(d,1H), 9.05(d1H), 9.35(s,1H) and 12.95(br s,1H).

(b) From 3-cyano-6-(3-phenanthryl)pyridin-2(1H)-one (1 g), the title compound (0.58 g) m.p. 294°C (decomp) after recrystallisation from dimethylformamide/water was prepared according to the method of Example 1(b) using N-methylpyrrolidinone as solvent; δ(DMSO-d_6), 7.20(d,1H), 7.64-8.17(m,7H), 8.56(d,1H), 9.08(d,1H) and 9.39(s,1H).

Example 6

6-(2-Quinolinyl)-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 2-acetylquinoline (0.63 g) (Y. Yamamoto nd A.Yanagi, Chem. Pharm. Bull.,1982, 30, 2003), 3-cyano-6-(2-quinolinyl)pyridin-2(1H)-one (0.35 g) m.p. 282-284°C after recrystallisation from ethanol, was

prepared according to the method of Example 1(a).

(b) From 3-cyano-6-(2-quinolinyl)pyridin-2(1H)-one (0.3 g), the title compound (0.06 g) m.p. 291-292°C (decomp) after recrystallisation from n-butanol was prepared according to the method of Example 1(b), using N-methylpyrrolidinone as solvent; δ(DMSO-d_6), 7.59(d,1H), 7.73(dt,1H), 7.89(dt,1H), 8.09(d,1H), 8.23(d,1H), 8.36(d,1H) and 8.63(d,1H).

Example 7

6-[1-(4-Methoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) From 4-methoxy-1-acetonaphthone (15 g) (E.A.Dixon, A.Fischer and F.P.Robinson, Can. J. Chem., 1981, 59, 2629), 3-cyano-6-[1-(4-methoxy)naphthyl]pyridin-2(1H)-one (16.1 g) m.p. 259-260°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(a).

(b) From 3-cyano-6-[1-(4-methoxy)naphthyl]pyridin-2(1H)-one (0.55 g), the title compound (0.35 g) 308-310°C (decomp) after recrystallisation from n-butanol,was prepared according to the method of Example 1(b) using N-methylpyrrolidinone as solvent; δ(DMSO-d_6), 4.05(s,3H), 6.63(d,1H), 7.10(d,1H), 7.57-7.66(m,3H), 7.88-7.95(m,1H), 8.24-8.30(m,1H) and 8.33(d,1H).

Example 8

3-Carboxy-6-(2-naphthyl)pyridin-2(1H)-one

3-Cyano-6-(2-naphthyl)pyridin-2(1H)-one (10 g) was refluxed in a mixture of acetic acid (250 ml) and 60% hydrobromic acid (250 ml) for 4 hours. The cooled

reaction mixture was poured into water (500 ml), the precipitated product separated by filtration, and washed thoroughly with water. Recrystallisation from dimethylformamide/ethanol gave the title compound (7.9 g) m.p. 319-320°C

Example 9

3-Carboxy-6-(1-naphthyl)pyridin-2(1H)-one

The title compound (0.6 g) m.p. 277-279°C after recrystallisation from ethanol, was prepared from 3-cyano-6-(1-naphthyl)pyridin-2(1H)-one (1 g)using the method of example 8.

Example 10

Ethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) A mixture of 3-cyano-6-(2-naphthyl)pyridin-2(1H)-one (40.9 g) and 90% orthophosphoric acid (300 ml) were heated to 180°C for 6 hours. The cooled reaction mixture was poured into water (500 ml), to precipitate 6-(2-naphthyl)-pyridin-2(1H)-one (30.8 g) as an off-white solid that was recrystallised from ethanol m.p. 253-255°C.

(b) Lithium diisopropylamide (from diisopropylamine 2.53g and n-butyl lithium 12.5ml of 2.0M in hexanes) was added over 5 minutes to a suspension of 6-(2-naphthyl)pyridin-2(1H)-one (5.5 g) in tetrahydrofuran (30 ml) at -78°C under a nitrogen atmosphere. When the addition was complete the reaction mixture was stirred at 0°C for 30 minutes, recooled to -78°C and treated with diethyl-chlorophosphate (4.3 g). After rewarming to 0°C stirring for 30 minutes, recooling to -78°C and addition of more

lithium diisopropylamide (from diisopropylamine 2.53g and n-butyl lithium 12.5ml of 2.0M in hexanes), the reaction mixture was stirred at -78°C for 90 minutes and at 0°C for 30 minutes before quenching with 2N HCl (50 ml). Tetrahydrofuran was removed at reduced pressure, the aqueous phase extracted with dichloromethane (3x100 ml), the combined organic extracts washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$), filtered and solvent removed at reduced pressure. The residue was chromatographed (silica gel, ethyl acetate-5% ethanol/ethyl acetate eluant) to give, after recrystallisation from ethyl acetate, diethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.8 g) m.p. 148-151°C.

(c) Diethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.0 g) and sodium hydroxide (1.2 g) were boiled together in water/ethanol (20ml 1:1) for 12 hours. Solvent was removed at reduced pressure, the residue dissolved in water, cooled to 0°C and concentrated hydrochloric acid added to pH1. The precipitate was separated by filtration and recrystallised from ethanol to give the title compound (0.54 g) m.p. 242-244°C

Example 11

n-Butyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Di-n-butyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (2 g) was prepared from 6-(2-naphthyl)-pyridin-2(1H)-one (2.2 g) and di-n-butylchlorophosphate (2.2 g) according to the method of Example 10(b); δ(DMSO-d_6) 0.88(t,6H), 1.30-1.44(m,4H), 1.55-1.66 (m,4H), 4.04(q,4H), 6.90(dd,1H), 7.59-7.67(m,2H), 7.89-8.06(m,5H) and 8.47(s,1H).

(b) From di-n-butyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (2 g) the title compound (0.12 g) m.p. 216-218°C after recrystallisation from water adjusted to pH1 with concentrated hydrochloric acid, was prepared according to the method of Example 10(c).

Example 12

n-Hexyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Di-n-hexyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1 g) was prepared from 6-(2-naphthyl)pyridin-2(1H)-one (2.2 g) and di-n-hexyl chlorophosphate (2.5 g) (B. Colin, N.M.Jones, C.McGuigan and P.A.Riley, Nucleic Acids Res., 1989, 17, 7195) according to the method of Example 10(b); $\delta(CDCl_3)$ 0.79(t,6H), 1.13(m,12H), 1.48(m,4H), 3.89-4.09(m,4H), 6.78(dd,1H), 7.56(m,2H), 7.86-8.00(m,3H), 8.17(m,1H), 8.24(dd,1H), 8.53(s,1H) and 13.15(br s,1H).

(b) From di-n-hexyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1 g) the title compound (0.33 g) m.p. 175-178°C after recrystallisation from ethanol, was prepared according to the method of Example 10(c).

Example 13

Phenyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Diphenyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.1 g) m.p. 200-201°C after recrystallisation from ethanol, was prepared from 6-(2-naphthyl)pyridin-2(1H)-one (1.1 g) and diphenyl-chlorophosphate (1.34 g) according to the method of

Example 10(b).

(b) From diphenyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1 g), the title compound (0.27 g) m.p. 236°C after recrystallisation from ethanol, was prepared according to the method of Example 10(c).

Example 14

Ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) 6-(1-naphthyl)pyridin-2(1H)-one (41.8 g) m.p. 219-220°C after recrystallisation from sec-butanol, was prepared from 3-cyano-6-(1-naphthyl)pyridin-2(1H)-one (50 g) according to the method of Example 10(a).

(b) Diethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (5.55 g) m.p. 220-222°C after re-crystallisation from ethanol/water, was prepared from 6-(1-naphthyl)pyridin-2(1H)-one (5.5 g) and diethyl chlorophosphate (4.3 g) according to the method of Example 10(b).

(c) From diethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1 g), the title compound (0.28 g) m.p. 257-258°C after recrystallisation from ethanol, was prepared according to the method of Example 10(c).

Example 15

n-Butyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Di-n-butyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-

pyridyl]phosphonate (1.45 g) m.p. 161-163°C after recrystallisation from ethanol, was prepared from 6-(1-naphthyl)pyridin-2(1H)-one (2.21 g) and di-n-butyl chlorophosphate (2.28 g) according to the method of Example 10(b).

(b) From di-n-butyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.45 g) the title compound (0.55 g) m.p. 202-204°C after recrystallisation from ethanol was prepared according to the method of Example 10(c).

Example 16

n-Hexyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Di-n-hexyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (2.1 g) isolated as an oil, was prepared from 6-(1-naphthyl)pyridin-2(1H)-one (2.21 g) and di-n-hexyl chlorophosphate (2.84 g) according to the method of Example 10(b); δ(DMSO-d_6) 0.85(t,6H), 1.21-1.45(m,12H), 1.57-1.71(m,4H), 4.04(m,4H), 6.45(m,1H), 7.53-8.11(m,8H) and 11.42(br s,1H).

(b) From di-n-hexyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.2 g) the title compound (0.35 g) m.p. 189-192°C after recrystallisation from ethanol, was prepared according to the method of Example 10(c).

Example 17

Ethyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) 6-(9-Phenanthryl)pyridin-2(1H)-one (5.98 g) m.p. 278-280°C after recrystallisation from n-butanol, was

prepared from 3-cyano-6-(9-phenanthryl)pyridin-2(1H)-one (8 g) according to the method of Example 10(a).

(b) Diethyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (2.46 g) was prepared from 6-(9-phenanthryl)pyridin-2(1H)-one (3 g) and diethyl chlorophosphate (2.27 g) according to the method of Example 10(b); δ(DMSO-d_6) 1.29(t,6H), 4.05-4.21(m,4H), 6.52(m,1H), 7.65-8.13(m,8H), 8.93(t,2H) and 12.3(br s,1H).

(c) From diethyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (2.46 g) the title compound (1.05 g) m.p. 253-255°C after recrystallisation from n-butanol, was prepared according to the method of Example 10(c).

Example 18

Ethyl 2-hydroxy-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate

(a) 6-(2-Naphthyl)pyridin-2(1H)-one (17.6 g) and dimethylformamide dimethylacetal (10.71 g) were heated together at 120°C in dimethylformamide (50 ml) for 4 hours. The brown solution was cooled to room temperature, diluted with ethyl acetate (300 ml) and washed with water (6x100 ml). The residue after removing solvent was column chromatographed (silica gel, hexane-20% dichloromethane/hexane eluant) to give 2-methoxy-6-(2-naphthyl)pyridine (12.4 g) which was recrystallised from ethanol m.p. 91°C

(b) To 2-methoxy-6-(2-naphthyl)pyridine (7.08 g) in tetrahydrofuran (50 ml) under nitrogen at -78°C methyl lithium (42ml of 1.5M in diethyl ether) was added over 10 minutes, followed by diisopropylamine (0.3 ml). The reaction mixture was stirred for 3 hours at 0°C, trans-

ferred into a solution of ethyl pyruvate (6.96 g) in tetrahydrofuran at -78°C and stirred for a further 1 hour at -78°C. After quenching with saturated ammonium chloride, the reaction mixture was diluted with ethyl acetate (250 ml), washed with water (2x100 ml), dried ($MgSO_4$) and solvent removed. The residue was column chromatographed (silica gel, 30% hexane/dichloromethane-dichloromethane eluant) to give ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate (6.05 g) which was recrystallised from ethanol m.p. 136-137°C

(c) To a solution of ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate (0.1 g) in acetonitrile (5 ml) containing sodium iodide (0.75 g) chlorotrimethyl-silane (0.54 g) was added. After stirring for 1 hour the reaction mixture was diluted with ethyl acetate (50 ml), washed with 5% sodium metabisulphite (20 ml) and water (20 ml), dried ($MgSO_4$) and solvent removed at reduced pressure. Recrystallisation of the residue from ethanol gave the title compound (0.06 g) m.p. 162-163°C.

Example 19

2-Hydroxy-2-[6-(2-Naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-propionic acid

(a) A solution of ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate in ethanol/2N sodium hydroxide (1:1, 8 ml) was boiled for 20 minutes. Solvent was removed at reduced pressure, the residue dissolved in water (50 ml), washed with ethyl acetate (2x30 ml), acidified with 2N hydrochloric acid and extracted with dichloromethane (5x50 ml). The combined extracts were washed with water (2x50 ml), dried ($MgSO_4$) and solvent removed to give 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionic acid (300m g) m.p. softens 242-244°C

(decomp); δ(DMSO-d_6) 1.59(s,3H), 4.00(s,3H), 7.55 (m,2H), 7.75(d,1H), 7.92-8.07(m,4H), 8.27(dd,1H) and 8.65(s,1H).

(b) 2-Hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]-propionic acid (0.4 g) was treated with sodium iodide (1.54 g)and chlorotrimethylsilane (1.08 g) according to the method of Example 18(c) to give after recrystallisation from ethanol the title compound (0.26 g) m.p. 218-222°C (decomp).

Example 20

2-Hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid

(a) Following the method of Example 18(b) 2-methoxy-6-(2-naphthyl)pyridine (2.36 g) was reacted with diethyl oxalate (3.65 g). Work up and column chromatography (silica gel, 70% hexane/dichloromethane-30% hexane/dichloromethane eluant) gave, after recrystallisation from ethyl acetate/hexane, ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (2.9 g) m.p 83-85°C.

(b) A solution of ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (0.61 g) in dichloromethane/ethanol/acetic acid (5:5:1,11 ml) at 0°C was treated with sodium borohydride (200 mg) in portions over 30 minutes. After stirring for a further 30 minutes, the reaction mixture was diluted with dichloromethane (50 ml), washed with water (3x30 ml), dried (MgSO4) and solvent removed. The residue was column chromatographed (silica gel, 20% hexane/dichloromethane eluant) to give ethyl 2-hydroxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (530 mg) m.p. 89-90°C.

(c) A solution of ethyl 2-hydroxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (530 mg) in ethanol/2N sodium hydroxide (1:1 8 ml) was stirred for 24 hour and boiled for a further 2 hours. Solvent was removed, the residue dissolved in water (50 ml), acidified with 2N hydrochloric acid and extracted with ethyl acetate (4x50 ml). The combined extracts were washed with water (2x50 ml), dried ($MgSO_4$) and solvent removed to give 2-hydroxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (480 mg) m.p. 164-165°C.

(d) 2-Hydroxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (0.46 g) and sodium thiomethoxide (0.5 g) were heated together in dimethylformamide (5 ml) at 100°C for 3 hours. The mixture was cooled (ice bath), water (5 ml) added and adjusted to pH4 with 2N hydrochloric acid. The precipitated solid was separated by filtration, washed (2x10ml 2N hydrochloric acid, 4x15ml water and 2x20ml diethyl ether) and recrystallised from ethanol to give the title compound (0.23 g) m.p. 239-240°C.

Example 21

2-Methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid

(a) To a solution of ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (1.0 g) in dimethylformamide (5 ml) sodium hydride (0.15g,50% in oil) was added. When gas evolution had ceased, iodomethane (0.57 g) was added the reaction mixture stirred for 2 hours, quenched carefully with water, diluted with ethyl acetate (50 ml), washed with water (6x50 ml), dried ($MgSO_4$) and solvent removed. The residue was column chromatographed (silica gel, 50% hexane/dichloromethane eluant) to give ethyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate

(0.13 g) containing 30% of the corresponding methyl ester; δ(DMSO-d_6) 1.18(t,3H), 3.40(s,3H), 4.09(s,3H), 4.14 (q,2H), 5.06(s,1H), 7.52(m,2H), 7.78(m,2H) 7.92-8.09 (m,3H), 8.36(d,1H) and 8.66(s,1H) (for the ethyl ester).

(b) Ethyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (0.13 g) was hydrolysed using the method of Example 20(c) to give 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetic acid (0.12 g); δ(DMSO-d_6) 3.36(s,3H), 4.06(s,3H), 7.56(m,2H), 7.79(m,2H), 7.92-8.07 (m,3H), 8.28(dd,1H) and 8.67(s,1H).

(c) Treatment of 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetic acid (0.12 g) with sodium iodide (1.42 g) and chlorotrimethylsilane (1.3 ml) in acetonitrile according to the method of example 18(c) gave, after recrystallisation from ethanol the title compound (0.07 g) m.p. 219-220°C (decomp).

Example 22

2-Propoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid

(a) A suspension of potassium hydroxide (0.45g,crushed pellets) was stirred in dimethylsulphoxide for 5 minutes. Ethyl 2-hydroxy-[6-(2-naphthyl)-2-methoxy-3-pyridyl)acetate (0.674 g) was then added followed after 3 minutes by iodopropane (0.51 g). Stirring was continued for 16 hours, water (1 ml) added and stirring continued for a further 3 hours. The reaction mixture was diluted with ethyl acetate (50 ml), acidified with 2N hydrochloric acid, washed with water (6x50 ml), dried (MgSO4) and solvent removed. The residue was column chromatographed (silica gel, dichloromethane-15% ethanol/dichloromethane eluant) to give 2-propoxy-2-[6-(2-

naphthyl)-2-methoxy-3-pyridyl]acetic acid (0.27 g); δ(DMSO-d_6) 0.87(t,3H), 1.47-1.65(m,2H), 3.32-3.61 (m,2H), 4.05(s,3H), 5.01(s,1H), 7.51-7.59(m,2H), 7.78 (2H,ABq), 7.90-8.05(m,3H), 8.27(dd,1H) and 8.65(s,1H).

(b) Treatment of 2-propoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetic acid (0.25 g) with sodium iodide (1.5 g) and chlorotrimethylsilane (1.08 g) in acetonitrile (5 ml) according to the method of Example 18(c) gave after recrystallisation from ethanol the title compound (0.085 g) m.p. 118-119°C(softens); δ(DMSO-d_6) 0.89(t,3H), 1.50-1.63(m,2H), 3.33-3.64(m,2H), 4.97(s,1H), 6.80(d,1H), 7.55-7.65(m,3H), 7.86(dd,1H), 7.94-8.04(m,3H), 8.38(s,1H) and 12.47(br s,1H).

Example 23

Ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

Treatment of ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (0.337 g) with sodium iodide (1.54 g) and chlorotrimethylsilane (1.08 g) in acetonitrile (10 ml) according to the method of Example 18(c) gave after recrystallisation from ethanol the title compound (0.23 g) m.p. 167-168°C.

Example 24

[6-(2-Naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphonic acid sodium salt

(a) Following the method of Example 18(b) 2-methoxy-6-(2-naphthyl)pyridine (1.88 g) was reacted with sulphuryl chloride (2.7 g). After the addition of the anion of 2-methoxy-6-(2-naphthyl)pyridine to sulphuryl chloride was

complete, the reaction mixture was stirred for a further 10 minutes at -78°C, quenched with 2N hydrochloric acid, diluted with ethyl acetate (200 ml), washed with water (50 ml), dried ($MgSO_4$) and solvent removed. The residue was stirred at room temperature in ethanol/2N sodium hydroxide (2:1 18 ml) for 16 hours and boiled for 2 hours. Acidification with 2N hydrochloric acid gave a solid which was separated by filtration, washed with ethyl acetate (2x20 ml) and recrystallised from ethanol/water to give [6-(2-naphthyl)-2-methoxy-3-pyridyl]sulphonic acid (0.35 g); δ(DMSO-d_6) 4.06(s,3H), 7.56(m,2H), 7.70 (d,1H), 7.91-8.09(m,4H), 8.27(dd,1H) and 8.68(s,1H).

(b) [6-(2-naphthyl)-2-methoxy-3-pyridyl]sulphonic acid (0.314 g) was heated with sodium thiomethoxide (0.4 g) in dimethylformamide (3 ml) at 100°C for 3 hours. Water (5 ml) was added followed by 2N hydrochloric acid to pH1, the mixture filtered, water removed at reduced pressure, the residual dimethylformamide refiltered diluted with water (10 ml) and cooled to 0°C for 30 days. The title compound (0.08 g) was separated by filtration m.p. >325°C; δ(DMSO-d_6) 7.17(br s,1H), 7.58(m,2H), 7.88-8.05(m-5H) and 8.49(s,1H).

Example 25

2-Oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

(a) Treatment of 6-(1-naphthyl)pyridin-2(1H)-one (17.64 g) with dimethylformamide dimethylacetal (19.04 g) according to the method of Example 18(a) gave after column chromatography (silica gel, 80% hexane/dichloromethane eluant) and recrystallisation from ethyl acetate/hexane, 2-methoxy-6-(1-naphthyl)pyridine (6.81 g) m.p. 56-58°C.

Or

A mixture of 6-(1-naphthyl)pyridin-2(1H)-one (4.41 g) and trimethylphosphite (20 ml) was heated at 180°C (oil bath temperature) for 40 minutes. The mixture was cooled to room temperature, diluted with ethyl acetate (100 ml) and washed with water (5x100 ml), dried ($MgSO_4$), and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 1:1 hexane/dichloromethane eluant) to give 2-methoxy-6-(1-naphthyl)pyridine.

(b) Following the method of Example 18(b) 2-methoxy-6-(1-naphthyl)pyridine (0.7 g) was reacted with diethyl oxalate. Work up and column chromatography (80% hexane/dichloromethane) gave, after recrystallisation from ethyl acetate/hexane ethyl 2-oxo-[2-methoxy-6-(1-naphthyl)-3-pyridyl] acetate (0.68 g) m.p. 70-72°C

(c) A solution of ethyl 2-oxo-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (0.4 g) in concentrated hydrochloric acid (4 ml) was heated to 110°C for 40 minutes. On cooling the precipitated solid was separated by filtration and washed with water to give the title compound (0.21 g) m.p. 228-230°C.

Example 26

Ethyl 2-oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetate

A mixture of ethyl 2-oxo-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (0.6 g) and sodium iodide (2.7 g) were heated together at reflux in chlorotrimethylsilane (2.3 ml) for 24 hours. The reaction mixture was quenched with 2N hydrochloric acid (10 ml), stirred for 1 hour and filtered. The residue was washed with water (2x20 ml)

and ethanol (2x5 ml) and recrystallised from acetone to give the title compound (0.2 g) m.p. 182-186°C.

Example 27

[6-(2-Naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

(a) To a suspension of 3-cyano-6-(2-naphthyl)pyridin-2(1H)-one (17 g) in tetrahydrofuran (100 ml) under nitrogen at -78°C, methyl lithium (100ml,1.4M in diethyl ether) was added over 30 minutes. After stirring for a further 20 minutes at -78°C, the reaction mixture was warmed to 0°C and stirring continued for 90 minutes. The reaction was quenched by the careful addition of saturated aqueous ammonium chloride (5 ml), followed by 2N hydrochloric acid (100 ml). The organic solvents were removed at reduced pressure and the yellow solid separated by filtration to give 3-acetyl-6-(2-naphthyl)pyridin-2(1H)-one (17.41 g) which was further purified by recrystallisation from acetonitrile/water m.p. 226-230°C.

Or

(b) A solution of 2-acetonaphthone (17.0 g) in dimethylformamide (10 ml) containing dimethylformamide dimethylacetal (12 g) was heated at reflux for 4 hours cooled to room temperature and poured into diethyl ether (250 ml). The precipitate was separated by filtration washed with diethyl ether and air dried to give 3-dimethylamino-1-(2-naphthyl)prop-2-ene-1-one 18.75g m.p. 110-112°C.

A mixture of 3-dimethylamino-1-(2-naphthyl)prop-2-ene-1-one (5.73 g), acetoacetamide (2.6 g) and sodium methoxide (2.81 g) in dimethylformamide (50 ml) was boiled for 8 hours, poured into 1N sodium hydroxide solution

(500 ml), washed with ethyl acetate (2x100 ml) and diethyl ether (3x100 ml). The solution was acidified with concentrated hydrochloric acid, filtered and the residue washed with water and dried to give 3-acetyl-6-(2-naphthyl)pyridin-2(1H)-one (1.37 g).

(c) A mixture of 3-acetyl-6-(2-naphthyl)pyridin-2(1H)-one (1.3 g), sulphur (0.23 g) and morpholine (0.64 ml) were heated on an oil bath at 150°C for 5 hours. The dark semi-solid was suspended in water (100 ml), sodium hydroxide (2 g) added and the mixture boiled for 30 minutes. After filtration, the solution was adjusted to pH5 with acetic acid and the precipitated product separated by filtration and washed with water, to give the title compound (0.47 g) m.p. 280-285°C.

Example 28

[6-(1-Naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

(a) 3-Acetyl-6-(1-naphthyl)pyridin-2(1H)-one (10.8 g) m.p. 239-240°C after recrystallisation from ethanol, was prepared from 3-cyano-6-(1-naphthyl)pyridin-2(1H)-one (12.3 g) according to the method of Example 27(a).

(b) To a suspension of 3-acetyl-6-(1-naphthyl)pyridin-2(1H)-one (6.0 g) in morpholine (4mls) sulphur (1.5 g) was added, the mixture was boiled for 4 hours and stood at room temperature overnight. The resultant black mixture was boiled in 2N sodium hydroxide (75 ml) for 4 hours, diluted with water (100 ml), treated with decolourising charcoal and filtered. Addition of carbon dioxide to pH7, refiltration and finally adjustment to pH5 with acetic acid, filtration of the precipitated product and recrystallisation from acetonitrile/water gave the title

compound (2.17 g) m.p. 203-207°C.

Example 29

7-Aza-6-(1-naphthyl)benzofuran-2-one

[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid (1.56 g) was boiled in acetic anhydride (20mls) until a clear solution was obtained. The solution was evaporated to dryness, the residue dissolved in diethyl ether (100 ml), washed with 5% sodium bicarbonate solution (3x50 ml), water (50 ml) saturated ammonium chloride solution (50 ml) and dried ($MgSO_4$). Removal of solvent gave a red solid which was continuously extracted with hexane for 16 hours. Concentration of the hexane to a small volume gave the title compound (0.88 g) m.p. 150-153°C.

Example 30

4-Ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)-pyridine

A mixture of ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl)phosphonate (0.66 g) silver carbonate (1.4 g) and diiodomethane (0.8 g) in dimethylformamide (4 ml) was heated at 100°C for 24 hours in the dark. More silver carbonate (0.7 g) and diiodomethane (0.4 g) were added and heating continued for a further 24 hours. The reaction mixture was diluted with ethyl acetate (50 ml), filtered, the filtrate washed with water (6x50 ml), dried ($MgSO_4$) and solvent removed. The residue was column chromatographed (silica gel, dichloromethane eluant), the appropriate fractions combined, and solvent removed, to give after recrystallisation twice from ethanol the title compound (0.1 g) m.p. 140-142°C.

Example 31

Ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonothioate

(a) To a solution of ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl)phosphonate (0.66 g), carbon tetrachloride (1.54 g) and aniline (0.93 g) in pyridine (5 ml) under nitrogen at 0°C, triethylphosphine (0.94 g) was added. The reaction mixture was stirred for 24 hours additional carbon tetrachloride (0.77 g) and triethylphosphine (0.47 g) added and stirring continued for a further 48 hours. Dilution with ethyl acetate (50 ml), washing with 2N hydrochloric acid (2x50 ml), water (4x50 ml) drying ($MgSO_4$) and removal of solvent gave a solid (0.18 g). The combined aqueous phases were extracted with dichloromethane (4x50 ml), the combined dichloromethane extracts washed with water (2x50 ml), dried ($MgSO_4$) and solvent removed. The residue was combined with the solid obtained from the ethyl acetate phase, column chromatographed (silica gel, dichloromethane eluant) the appropriate fractions combined, solvent removed and the residue recrystallised twice from ethanol to give O-ethyl-N-phenyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonoamidate (0.13 g) m.p. 258-260°C.

Or

(b) To a suspension of ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.65 g) in dichloromethane (15 ml), dimethylformamide (0.05 ml) was added followed by oxalyl chloride (2.5 ml). When gas evolution had ceased solvent was removed and the residue redissolved in dichloromethane (20 ml), cooled (ice bath) and aniline (0.9 g), followed by triethylamine (1.2 g) added. After stirring for 2 hours at 0°C the reaction mixture was

diluted with dichloromethane (50 ml), washed with 2N hydrochloric acid (2x50 ml) and water (2x50 ml), dried ($MgSO_4$) and solvent removed. The residue was chromatographed (dichloromethane-5% ethanol/dichloromethane eluant) the appropriate fractions combined, solvent removed and the residue recrystallised twice from ethanol to give O-ethyl-N-phenyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonoamidate (0.4 g).

(c) O-Ethyl-N-phenyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonoamidate (0.4 g) was added in portions over 5 minutes to a suspension of sodium hydride (0.2g, 50% in oil washed with hexane) in dimethoxyethane. The mixture was stirred at room temperature for 1 hour and at 50°C for 15 minutes, cooled (ice bath), and carbon disulphide (0.76 g) added. The mixture was stood at room temperature for 14 days, diluted with ethyl acetate, washed with 2N hydrochloric acid (2x30 ml) and water (2x30 ml) dried ($MgSO_4$) and solvent removed. The combined aqueous washes were combined and extracted with dichloromethane (3x50 ml) the combined extracts washed with water (50 ml) dried ($MgSO_4$) solvent removed and the residue combined with the ethyl acetate soluble material. The combined organic material was recrystallised twice from ethanol to give the title compound (0.09 g) m.p. 200-202°C.

Example 32

3-Methoxycarbonyl-6-(2-naphthyl)pyridin-2(1H)-one

3-Carboxy-6-(2-naphthyl)pyridin-2(1)-one (1 g), was added to thionyl chloride (100 ml) and the mixture boiled for 4 hours. Excess thionyl chloride was removed at reduced pressure and the solid red residue stirred in

methanol (50 ml) overnight. The precipitated solid was separated by filtration and recrystallised from methanol to give the title compound (0.55 g) m.p. 223-226°C.

Example 33

Ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate

(a) Ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate (0.9 g) was treated with sodium hydride (0.15g, 50% in oil) and iodomethane (0.56 g) according to the method of Example 21(a). Purification by column chromatography (silica gel, 20% hexane/dichloromethane eluant) gave ethyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate (0.76 g) as a pale yellow oil containing 25 molar% of methyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate; δ(DMSO-d_6) 1.15(t,3H), 1.61(s,3H), 3.25(s,3H), 3.99(s,3H), 4.15 (m,2H), 7.54-7.58(m,2H), 7.78(d,1H), 7.93-8.08(m,4H), 8.26 (d,1H) and 8.66(s,1H) (for the ethyl ester).

(b) Ethyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]propionate (0.75 g) was treated with sodium iodide (1.54 g) and chlorotrimethylsilane (1.08 g) according to the method of Example 18(c) to give after recrystallisation from ethanol the title compound (0.42 g) m.p. softens 141-145°C, melts 166-169°C containing 25 molar% of methyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]-propionate; δ(DMSO-d_6) 1.15(t,3H), 1.56(s,3H), 3.25 (s,3H), 4.09(q,2H), 6.77(d,1H), 7.57-7.60(m,2H), 7.67 (d,1H), 7.82-8.03(m,4H), 8.36(s,1H) and 11.98(br s,1H) (for the ethyl ester).

Example 34

3-(5-Tetrazolyl)-6-[2-(1-propyloxy)naphthyl]pyridin-2(1H)-one

(a) 1-Hydroxy-2-acetonaphthone (9.3 g) 1-iodopropane (17 g) and potassium carbonate (6.9 g) were combined in dimethylformamide (40 ml) and heated to 120°C for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (200 ml), washed with water (6x100 ml), dried ($MgSO_4$) and solvent removed to give 1-propyloxy-2-acetonaphthone (10.9 g) as a brown oil; δ(DMSO-d_6) 1.07(t,3H), 1.89(m,2H), 2.70(s,3H), 3.96(t,2H), 7.62-7.69(m,3H), 7.75(d,1H), 7.97(m,1H) and 8.19(m,1H).

(b) 1-Propyloxy-2-acetonaphthone (10.9 g) and dimethylformamide dimethylacetal (6.55 g) were combined in dimethylformamide and heated at 130°C for 18 hours. The deep red solution was cooled to room temperature, cyanoacetamide (4.2 g) added and the solution boiled for 36 hours. The cooled reaction mixture was poured into water (200 ml) containing acetic acid (5 ml) and stirred for 30 minutes, ethanol (100 ml) was then added and stirring continued for a further 30 minutes. The precipitate was separated by filtration and purified by column chromatography (silica gel, dichloromethane-10% ethanol/dichloromethane) to give after recrystallisation from ethanol, 3-cyano-6-[2-(1-propyloxy)naphthyl]-pyridin-2(1H)-one (0.98 g) m.p. 220-223°C.

(c) From 3-cyano-6-[2-(1-propyloxy)naphthyl]pyridin-2(1H)-one (0.6 g), the title compound (0.27 g) m.p. 269°C (decomp) after recrystallisation from n-butanol, was prepared according to the method of Example 1(b) using N-methylpyrrolidinone as solvent; δ(DMSO-d_6),

0.93(t,3H), 1.66-1.74(m,2H), 3.79(t,2H), 6.81(d,1H), 7.62(d,1H), 7.65-7.69(m,2H), 7.85(d,1H), 8.01-8.05(m,1H), 8.20-8.24(m,1H) and 8.57(d,1H).

Example 35

6-[2-(1-Pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) 1-Pentyloxy-2-acetonaphthone (11.5 g) was prepared as an oil from 1-hydroxy-2-acetonaphthone (9.3 g) n-pentyl iodide (9.9 g) and potassium carbonate (6.9 g) according to the method of Example 34(a); $\delta(CDCl_3)$ 0.97(t,3H), 1.36-1.59(m,4H), 1.88-2.01(m,2H), 2.76(s,3H), 4.02(t,2H), 7.53-7.72(m,4H), 7.83(m,1H) and 8.20(m,1H).

(b) 3-Cyano-6-[2-(1-pentyloxy)naphthyl]pyridin-2(1H)-one (1.41 g) m.p. 141-143°C after recrystallisation from ethanol, was prepared from 1-pentyloxy-2-acetonaphthone (10.24 g), dimethylformamide dimethylacetal (5.24 g), cyanoacetamide (3.36 g) and sodium methoxide (4.32 g) according to the method of Example 1(a).

(c) From 3-cyano-6-[2-(pentyloxy)naphthyl]pyridin-2(1H)-one (0.99 g) the title compound (0.57 g) m.p. 209-212°C after recrystallisation from ethanol was prepared according to the method of Example 1(b) using N-methylpyrrolidinone as solvent.

Example 36

[6-(9-Phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

(a) 3-Acetyl-6-(9-phenanthryl)pyridin-2(1H)-one (1.63 g) m.p. 239-242°C after recrystallisation from ethanol, was

prepared from 3-cyano-6-(9-phenanthryl)pyridin-2(1H)-one (2.96 g) and methyl lithium (13ml, 1.5M in diethyl ether) according to the method of Example 27(a)

(b) From 3-acetyl-6-(9-phenanthryl)pyridin-2(1H)-one (1.5 g) sulphur (0.18 g) and morpholine (4 ml) the title compound (0.16 g) m.p. 301°C after recrystallisation from ethanol, was prepared according to the method of Example 27(c).

Example 37

2-Hydroxyethyl 2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylate

Ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]-acetate (1.0 g) and p-toluenesulphonic acid (0.1 g) were heated together in 1,2-ethanediol (4 ml) at 120°C for 6 hours. The clear solution was diluted with ethyl acetate (50 ml) washed with water (5x50 ml), dried ($MgSO_4$) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane - 6% ethanol/dichloromethane eluant), the appropriate fractions combined and solvent removed. Recrystallisation from ethanol gave the title compound (0.24 g) m.p. 212-215°C.

Example 38

2-[6-(2-Naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylic acid sodium salt

To a solution of 2-hydroxyethyl 2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylate (0.3 g) in ethanol (25 ml) sodium hydroxide solution (3ml of 2N) was added at room temperature. After 2 hours the precipitated solid was separated by filtration and the

residue washed with ethanol (3x10 ml) giving the title compound (0.27 g) m.p. >315°C; δ(DMSO-d_6) 3.98-4.19(m,4H), 6.83(d,1H), 7.64(m,2H), 7.78(d,1H), 7.88(d,1H), 7.98-8.10(m,3H) and 8.37(s,1H).

Example 39

n-Butyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate

(a) Di-n-butyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (0.38 g), was prepared from 6-(9-phenanthryl)pyridin-2(1H)-one (3 g) and di-n-butyl chlorophosphate (2.8 g) according to the method of Example 10(b); δ(DMSO-d_6) 0.91(t,6H), 1.17-1.47(m,4H), 1.57-1.67(m,4H), 4.07(q,4H), 6.54(m,1H), 7.67-8.16(m,8H) and 8.89-8.99(m,2H).

(b) From di-n-butyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (0.38 g) the title compound (0.13 g) m.p. 223-225°C, after recrystallisation from ethanol, was obtained according to the method of Example 10(c).

Example 40

3-(5-Tetrazolyl)-6-(3-thianaphthenyl)pyridin-2(1H)-one

(a) From 3-acetylthianaphthene (5 g), 3-cyano-6-(3-thianaphthenyl)pyridin-2(1H)-one (5.64 g) m.p. 302-303°C after recrystallisation from ethanol, was prepared according to the method of Example 1(a).

(b) From 3-cyano-6-(3-thianaphthenyl)pyridin-2(1H)-one (0.92 g), the title compound (0.88 g) m.p. 360°C (decomp)

after recrystallisation from n-butanol, was prepared according to the method of Example 1(b) using N-methyl-pyrrolidinone as solvent.

Example 41

6-(4-Quinolinyl)-3-(5-(tetrazolyl)pyridin-2(1H)-one

(a) From 4-acetylquinoline (1.02 g) (Y.Yamamoto and A.Yanagi, Chem. Pharm. Bull., 1982, 30, 2003), 3-cyano-6-(4-quinolinyl)pyridin-2(1H)-one (0.8 g) m.p. 318-320°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(a).

(b) From 3-cyano-6-(4-quinolinyl)pyridin-2(1H9-one (0.49 g), the title compound (0.4 g) m.p. 252-254°C after recrystallisation from n-butanol, was prepared according to the method of Example 1(b)

Example 42

6-[1-(4-Hydroxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) A solution of 3-cyano-6-[1-(4-methoxy)naphthyl]-pyridin-2(1H)-one (1.1 g) and sodium thiomethoxide (0.5 g) in dimethylformamide (5 ml) was heated at 130°C for 5 hours. The solution was cooled to room temperature acidified with 2N hydrochloric acid and purged with nitrogen to remove excess methanethiol. The precipitated yellow solid was separated by filtration to give 3-cyano-6-[1-(4-hydroxy)naphthyl]pyridin-2(1H)-one (0.62 g) m.p. 297-300°C (decomp) after recrystallisation from ethanol.

(b) From 3-cyano-6-[1-(4-hydroxy)naphthyl]pyridin-2(1H)-one (0.52 g) the title compound (0.33 g) m.p. 313-315°C (decomp) after recrystallisation from ethanol, was prepared according to the method of Example (1b) using N-methylpyrrolidinone as solvent.

Example 43

2-Methoxyethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate

a) To a solution of phosphoryl chloride (5.9 ml) in diethyl ether (30 ml) at 0°C, a solution of triethylamine (13 ml) and 2-methoxyethanol (9.8 ml) in diethyl ether (30 ml) was added over 30 minutes. The mixture was stirred at room temperature over night, filtered and solvent removed at reduced pressure to give di-2-(methoxyethyl) chlorophosphate (13.7 g) as an oil which was used without further purification δ(DMSO-d_6) 3.41(s,6H), 3.59-3.72(m,4H) and 4.32(m,4H).

b) Di-(2-methoxyethyl) [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.3 g) was prepared from 6-(2-naphthyl)pyridin-2(1H)-one (2.2 g) and di-(2-methoxy-ethyl) chlorophosphate (2.3 g) according to the method of Example 10(b) δ(DMSO-d_6) 3.23(s,6H), 3.36(t,4H), 4.04-4.16(m,4H), 6.73(dd,1H), 7.53-7.64(m,2H), 7.84-8.13(m,4H), 8.20(dd,1H) and 8.44(s,1H).

c) From di-(2-methoxyethyl) [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.3 g) the title compound (0.16 g) m.p. 220-221°C was prepared according to the method of Example 10(c).

Example 44

n-Propyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate.

(a) Di-n-propyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.5g) m.p.130-133°C was prepared from 6-(2-naphthyl)pyridin-2(1H)-one (2.2g) and di-n-propyl chlorophosphate (2.23g) according to the method of Example 10(b).

(b) From di-n-propyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.5g) the title compound (0.92g) m.p. 238-239°C after precipitation of the sodium salt from aqueous solution with 2N hydrochloric acid, was prepared according to the method of Example 10(c)

Example 45

n-Propyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate.

(a) Di-n-propyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (0.66g) m.p. 198°C after recrystallisation from ethanol, was prepared from 6-(9-phenanthryl)pyridin-2(1H)-one (1.08g) and di-n-propyl chlorophosphate (1.00g) according to the method of Example 10(b).

(b) From di-n-propyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (1.04g) the title compound (0.19g) m.p. 244-247°C after recrystallisation from n-propanol was prepared according to the method of Example 10(c).

Example 46

2-Hydroxy-2-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid.

(a) 2-Methoxy-6-(9-phenanthryl)pyridine (3g) m.p.105-106°C was prepared from 6-(9-phenanthryl)-pyridin-2(1H)-one (10g) according to the method of Example 18(a).

(b) Ethyl 2-oxo-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetate (2.5g) isolated as an oil, was prepared from 2-methoxy-6-(9-phenanthryl)pyridine 2.9g) according to the method of Example 20(a). $\delta(CDCl_3)$ 1.44(t,3H), 4.06(s,3H), 4.46(q,2H), 7.40(d,1H), 7.56-7.71(m,4H), 7.91(s,1H), 7.92(d,1H), 8.22(d,1H), 8.35(d,1H), 8.71(d,1H) and 8.77(d,1H).

(c) Ethyl 2-hydroxy-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetate (1.5g) was prepared from ethyl 2-oxo-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetate (2.5g) according to the method of Example 20(b). $\delta(CDCl_3)$ 1.29(t,3H), 3.68(d,1H), 4.02(s,3H), 4.30(q,2H), 5.33(d,1H), 7.26(d,1H), 7.54-7.74(m,4H), 7.87(s,1H), 7.93(dd,1H), 8.24(d,1H), 8.71(d,1H) and 8.77(d,1H).

(d) 2-Hydroxy-2-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetic acid (0.37g) was prepared from ethyl 2-hydroxy-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetate (0.50g) according to the method of Example 20(c). $\delta(d_6\text{-DMSO})$ 3.91(s,3H), 5.29(s,1H), 7.37(d,1H), 7.60-7.81(m,4H), 7.92(d,1H), 7.98(s,1H), 8.06(d,1H), 8.20(d,1H), 8.88(d,1H) and 8.94(d,1H).

(e) From 2-hydroxy-2-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetic acid (0.37g), the title compound (0.05g) m.p.206°C (decomp) after precipitation from basic solution with 2N hydrochloric acid, according to the method of Example 18(c). $\delta(d_6$-DMSO) 5.14(s,1H), 6.53(d,1H), 7.64-7.89(m,6H), 7.97(s,1H), 8.07(d,1H), 8.89(d,1H) and 8.95(d,1H).

Example 47

Ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

From ethyl 2-methoxy-2-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (0.75g), the title compound (0.53g) m.p. 177-179°C after recrystallisation from ethanol, was prepared according to the method of Example 18(c).

Example 48

Ethyl 2-methoxy-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

(a) From ethyl 2-oxo-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (5.6g), ethyl 2-hydroxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (2.4g) was prepared according to the method of Example 20(b). $\delta(CDCl_3)$ 1.27(t,3H), 3.67(d,1H), 4.04(s,3H), 4.33(q,2H), 5.31(d,1H), 7.23(d,1H), 7.45-7.92(m,7H) and 8.27(m,1H).

(b) From ethyl 2-hydroxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (2.4g), 2-hydroxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetic acid (2.01g) m.p.148-150°C, was prepared according to the method of Example 20(c).

(c) To a solution of 2-hydroxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetic acid (1g) in 20% aqueous dimethylsulphoxide (5ml), potassium hydroxide (crushed pellets, 0.56g) was added followed by iodomethane (0.85g). The mixture was stirred for 4 hours at room temperature, additional iodomethane (0.8g) added and stirring continued overnight. The reaction mixture was diluted with ethyl acetate (50ml), acidified with 2N hydrochloric acid and the organic phase washed with water (5x50ml). After removal of solvent the residue was boiled in ethanol (5ml) containing 2N sodium hydroxide (5ml) for 3 hours. The mixture was diluted with ethyl acetate and acidified with 2N hydrochloric acid, the organic phase was washed with water (2x30ml) and solvent removed to give 2-methoxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetic acid (0.63g). $\delta(CDCl_3)$ 3.52(s,3H), 4.04(s,3H), 5.12(s,1H), 7.23(d,1H), 7.49-7.93(m,7H) and 8.28(m,1H).

(d) To a solution of 2-methoxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetic acid (0.61g) in dimethylformamide (4ml) containing potassium carbonate (0.42g), iodoethane was added and the mixture stirred for 8 hours. The reaction mixture was diluted with ethyl acetate (30ml) washed with water (5x30ml) and solvent removed to give ethyl 2-methoxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (0.61g) as a yellow oil. $\delta(CDCl_3)$ 1.29(t,3H), 3.52(s,3H), 4.02(s,3H), 4.27(q,2H), 5.16(s,1H), 7.22(d,1H), 7.46-7.92(m,7H) and 8.27(m,1H).

(e) From ethyl 2-methoxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetate (0.6g), the title compound (0.3g) m.p.171-172°C after recrystallisation from ethanol was prepared according to the method of Example 18(c).

Example 49

Sodium 2-ethoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

(a) 2-Ethoxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (0.49g) isolated as an oil after column chromatography (silica gel, dichloromethane-10% ethanol/dichloromethane) was prepared from 2-hydroxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (0.55g) according to the method of Example 48(c) using iodoethane instead of iodomethane.

(b) From 2-ethoxy-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (0.47g), the title compound isolated as the sodium salt (0.32g) m.p.300-310°C (decomp) after recrystallisation from aqueous ethanol, was prepared according to the method of example 18(c). $\delta(d_6$-DMSO) 1.03(t,3H), 3.24-3.45(m,2H), 4.47(s,1H), 6.76(d,1H), 7.25-8.08(m,7H) and 8.39(s,1H).

Example 50

3-Carboxy-6-(9-phenanthryl)pyridin-2(1H)-one

From 3-cyano-6-(9-phenanthryl)pyridin-2(1H)-one (2g), the title compound (0.3g) m.p. >300°C after recrystallisation from ethanol/diethyl ether, was prepared according to the method of Example 8. $\delta(d_6$-DMSO) 6.92(d,1H), 7.69-7.93(m,5H), 8.09(s,1H), 8.11(d,1H), 8.52(d,1H), 8.95(d,1H) and 9.00(d,1H).

Example 51

6-[1-(4-Propoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one

(a) To a suspension of sodium hydride (60% dispersion in oil, 0.36g) in dimethylformamide (5ml), 3-cyano-6-[1-(4-hydroxy)naphthyl]pyridin-2(1H)-one (0.90g) in dimethylformamide (5ml) was added over 10 minutes. The reaction mixture was stirred until gas evolution ceased, iodopropane (0.35ml) added and stirring continued for 40 minutes. The mixture was diluted with water (30ml) and the precipitated product separated by filtration to give 3-cyano-6-[1-(4-propoxy)naphthyl]pyridin-2(1H)-one (0.63g) m.p.249°C after recrystallisation from ethanol.

(b) From 3-cyano-6-[1-(4-propoxy)naphthyl]pyridin-2(1H)-one (0.44g) 6-[1-(4-Propoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one (0.46g) m.p. 286-287°C after recrystallisation from n-butanol was prepared according to the method of Example (1b) using N-methylpyrrolidinone as solvent.

Example 52

Ethyl 2-hydroxy-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

From ethyl 2-hydroxy-[2-methoxy-6-(9-phenanthryl)-3-pyridyl]acetate (0.74g), the title compound (0.35g) m.p. 170-172°C after recrystallisation from ethanol, was prepared according to the method of Example 18(c).

Example 53

2-Oxo-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

From ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (0.2g) the title compound (0.17g) m.p.237.5°C (decomp) after precipitation from basic solution with 2N hydrochloric acid, was prepared according to the method of Example 25(c). $\delta(d_6$-DMSO) 7.00(d,1H), 7.58-7.72(m,2H), 7.88-8.13(m,4H), 8.25(d,1H), 8.52(s,1H) and 12.82(br. s,1H).

Example 54

2-Hydroxy-2-[6(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid

From 2-hydroxy-[2-methoxy-6-(1-naphthyl)-3-pyridyl]acetic acid (0.93g), the title compound (0.63g) m.p.198-199°C (decomp) after recrystallisation from ethyl acetate, was prepared according to the method of Example 18(c). $\delta(d_6$-DMSO) 5.13(s,1H), 5.83(br. s,1H), 6.43(d,1H), 7.53-7.68(m,5H), 7.77-7.83(m,1H) and 7.94-8.05(m,2H).

Example 55

n-Butyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

(a) n-Butyl 2-methoxy-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (0.9g) isolated as an oil after column chromatography (silica gel, 50%hexane/dichloromethane eluant) was prepared from 2-methoxy-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetic acid (0.96g), according to the

method of Example 48(d) using iodobutane (0.55g) instead of iodoethane. δ($CDCl_3$) 0.88(t,3H), 1.22-1.37(m,2H), 1.54-1.65(m,2H), 3.47(s,3H), 4.14(s,3H), 4.17(t,2H), 5.13(s,1H), 7.48-7.55(m,3H), 7.78-7.96(m,4H), 8.19(dd,1H) and 8.52(s,1H).

(b) From n-butyl 2-methoxy-[6-(2-naphthyl)-2-methoxy-3-pyridyl]acetate (0.85g) the title compound (0.63g) m.p.116-117°C after recrystallisation from ethyl acetate/hexane, was prepared according to the method of Example 18(c).

Example 56

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphinic acid sodium salt

(a) [6-(2-naphthyl)-2-methoxy-3-pyridyl]sulphinic acid (0.53g) was prepared from 2-methoxy-6-(2-naphthyl)pyridine (1.18g) according to the method of Example 18(b) using a saturated solution of sulphur dioxide in tetrahydrofuran (10ml) instead of ethyl pyruvate to quench the anion. δ(d_6-DMSO) 4.14(s,3H), 7.56-7.60(m,2H), 7.90-8.18(m,5H), 8.17(d,1H), 8.31(dd,1£H) and 8.74(s,1H).

(b) From [6-(2-naphthyl-2-methoxy-3-pyridyl]sulphinic acid (0.5g), [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphinic acid (0.33g) was prepared according to the method of Example 21(d). The sodium salt was prepared by dissolving [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphinic acid (0.33g) in water (5ml) containing sodium carbonate (0.053g)and subsequently removing solvent at reduced pressure. The residue was recrystallised from aqueous ethanol to give the title compound (0.3g) m.p. foams at 190°C. δ(d_6-DMSO) 7.40-7.62(m,4H), 7.92-8.14(m,4H) and 8.55(s,1H)

Example 57

Ethyl 2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate

(a) Diethylaminosulphur trifluoride (0.69g) was added to a solution of ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1g) in dichloromethane (30ml) the mixture was stirred at room temperature for 3 hours and poured onto ice (100g). The mixture was diluted with more dichloromethane (70ml), the organic phase separated, dried ($MgSO_4$) and solvent removed. The residue was column chromatographed (silica gel, 10% diethyl ether/petroleum ether eluant) to give ethyl 2,2-difluoro-2-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (0.93g) as an oil.$\delta(CDCl_3)$ 1.33(t,3H), 4.11(s,3H), 4.37(q,2H), 7.458.14(m,8H) and 8.53(s,1H).

(b) From ethyl 2,2-difluoro-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (0.63g) the title compound (0.205g), m.p.196-197°C after column chromatography (silica gel, dichloromethane eluant), was prepared according to the method of Example 18(c).

Example 58

2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid

(a) 2-Oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (1.3g) was prepared from ethyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1.5g) according to the method of Example 20(c). $\delta(CDCl_3)$ 3.96(s,3H), 7.25-7.39(m,2H), 7.47(d,1H), 7.61-7.80(m,3H), 7.98-8.10(m,3H) and 8.36(s,1H).

(b) Benzyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1.6g) was prepared from 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetic acid (1.3g) according to the method of Example 48(d) using benzyl bromide (0.86g) instead of iodoethane. $\delta(CDCl_3)$ 3.87(s,3H), 5.39(s,2H), 7.37-7.65(m,8H), 7.83-8.03(m,3H), 8.17(dd,1H), 8.28(d,1H) and 8.55(s,1H).

(c) Benzyl 2,2-difluoro-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1.2g) was prepared from benzyl 2-oxo-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1.6g) according to the method of Example 57(a). $\delta(CDCl_3)$ 3.87(s,3H), 5.32(s,2H), 7.36(s,5H), 7.49-7.60(m,3H), 7.82-7.99(m,4H), 8.15(dd,1H) and 8.51(s,1H).

(d) Benzyl 2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate (0.8g) was prepared from benzyl 2,2-difluoro-[2-methoxy-6-(2-naphthyl)-3-pyridyl]acetate (1.2g) according to the method of Example 18(c). $\delta(CDCl_3)$ 4.99(s,2H), 6.80(d,1H), 7.18(s,5H), 7.52-7.64(m,2H), 7.77-8.12(m,5H) and 8.26(s,1H).

(e) A solution of benzyl 2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate (0.6g) in ethanol/dichloromethane (25ml,4:1)was stirred for 2 hours at 15°C with 10% palladium on charcoal (0.1g) under hydrogen at atmospheric pressure. The reaction was filtered (celite pad), solvent removed at reduced pressure and the residual oil dissolved in 2N sodium hydroxide. The title compound (0.24g) m.p. 208°C (decomp) was obtained by acidification of the basic solution with conc. hydrochloric acid. $\delta(d_6\text{-DMSO})$ 6.87(d,1H), 7.59-7.63(m,2H), 7.84-8.07(m,5H) and 8.43(s,1H).

Example 59

4-(1-Naphthyl)salicylic acid

(a) m-Methoxyphenyl magnesium bromide was prepared in the usual way from magnesium (29g) and m-bromoanisole (220g) in tetrahydrofuran (180ml). After the addition of m-bromoanisole was complete the reaction mixture was boiled for 30 minutes added to 1-tetralone (168.12g) in tetrahydrofuran (120mls) and boiled for a further 1 hour. Acetic anhydride (150ml) was then added and the reaction mixture maintained at 60°C for 30 minutes, treated with water (100ml), the organic phase separated and dried. Distillation of the organic phase gave 3,4-dihydro-1-(3-methoxyphenyl)naphthalene (178g) bp 159-162°C/0.3mmHg.

(b) A mixture of 3,4-dihydro-1-(3-methoxyphenyl)-naphthalene (178g) and sulphur (27g) was heated at 250°C until evolution of gas ceased. Vacuum distillation gave a brown oil bp 156-160°C/0.4mmHg that was recrystallised from hexane to give 3-(1-naphthyl)anisole (102g) mp 40-44°C.

(c) To a solution of 3-(1-naphthyl)anisole (7.03g) in tetrahydrofuran (100ml) at -78°C under an inert atmosphere sec-butyl lithium (30ml 1.3M in cyclohexane) was added over 30 minutes. After the addition was complete the reaction mixture was stirred for a further 90 minutes then poured over solid carbon dioxide (200g) in tetrahydrofuran (500ml). The mixture was warmed to room temperature and treated with diethyl ether (100ml) and 5M hydrobromic acid (100ml). The organic phase was separated washed with water (2x100ml) dried ($MgSO_4$) and solvent removed to give 2-methoxy-4-(1-naphthyl)benzoic acid (6.6g) mp 152-155°C.

(d) A mixture of 2-methoxy-4-(1-naphthyl)benzoic acid glacial acetic acid (100ml) and 48% hydrobromic acid (500ml) was boiled for 5 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in 20% sodium bicarbonate (100ml), filtered and adjusted with 2N hydrochloric acid to pH4. The solid product was separated by filtration and recrystallised from acetonitrile/water to give the title compound (3.58g), mp 187-190°C.

Example 60

Ethyl 2-hydroxy-4-(1-naphthyl)phenyl phosphonate sodium salt

(a) To a solution of 3-(1-naphthyl)anisole (7.03g) in dichloromethane (100ml) at -78°C boron tribromide (1ml) was added, the mixture stirred at -78°C for 1 hour and then warmed to room temperature. After addition to saturated sodium acetate solution (100mls) the organic phase was separated and washed with water (50ml), saturated sodium bicarbonate solution (50ml) and saturated ammonium chloride solution (50ml) and dried ($MgSO_4$). The filtered solution was treated with triethylamine (6.0ml)and diethylchlorophosphate (5.8ml) and stirred at room temperature overnight. The solution was washed with water (50ml), saturated sodium bicarbonate (50ml) and saturated ammonium chloride (50ml) dried ($MgSO_4$) and solvent removed. The residue was dissolved in tetrahydrofuran (50ml) and added to a mixture of lithium diisopropylamide (18ml 1.5M in hexane) and tetrahydrofuran (50ml) at -78°C. The mixture was stirred for 10 minutes at -78°C and 25 minutes at 0°C, quenched with acetic acid (1ml) and saturated ammonium chloride solution (25ml) diluted with diethyl ether (100ml) the organic phase separated and washed with water

(2x50ml), dried ($MgSO_4$) and solvent removed. The colourless solid obtained was recrystallised from diethyl ether/hexane to give diethyl 2-hydroxy-4-(1-naphthyl)-phenyl phosphonate (4.76g) mp 170-173°C.

(b) A suspension of diethyl 2-hydroxy-4-(1-naphthyl)-phenyl phosphonate (2.0g) in 1N sodium hydroxide (40ml) was boiled for 4 hours cooled to room temperature and filtered. The filtrate was adjusted to pH5 with acetic acid the precipitated product separated by filtration and washed with water to give the title compound (1.84g) mp 168-170°C.

Example 61

5-[2-Hydroxy-4-(1-naphthyl)phenyl]tetrazole

(a) To a solution of 3-(1-naphthyl)anisole (7.04g) in tetrahydrofuran (40ml) at -78°C sec-butyl lithium (25ml 1.3M in cyclohexane) was added followed after 45 minutes by dimethylformamide (2.6ml). The solution was stirred at -78°C for a further 15 minutes and at room temperature for 30 minutes. The reaction was quenched with saturated ammonium chloride diluted with diethyl ether, the organic phase washed with saturated ammonium chloride, dried ($MgSO_4$) and solvent removed. The residue obtained was dissolved in ethanol (50ml), hydroxylamine hydrochloride (2.5g) and saturated sodium acetate (25ml) added and the mixture heated on the steam bath for 2 hours. The precipitate formed on cooling was separated by filtration washed with water and boiled in acetic anhydride (50ml) for 4 hours. The solution was poured into water (200ml) stirred for 1 hour and extracted with diethyl ether (4x150ml). The combined extracts were washed with water (50ml), 5% sodium bicarbonate solution (50ml) and saturated ammonium chloride (50ml), dried ($MgSO_4$) and

solvent removed. The residue was recrystallised from diethyl ether/hexane to give 2-cyano-5-(1-naphthyl)-anisole (4.74g) mp 100-103°C.

(b) To a solution of 2-cyano-5-(1-naphthyl)anisole (2.59g) in dimethylformamide (10ml) sodium azide (1.3g) and ammonium chloride (1.1g) were added. The mixture was boiled for 24 hours additional sodium azide (1.3g) and ammonium chloride (1.1g) added and heating continued for a further 48 hours. The mixture was poured into water (100ml) adjusted to pH10 with ammonium hydroxide and washed with diethyl ether (4x50ml). The aqueous solution was filtered and acidified with 2N hydrochloric acid. The precipitated material was separated by filtration, dried, suspended in dichloromethane (50ml) at -70°C and treated with boron tribromide (1ml). The reaction was stirred for 2 hours at -70°C and for 2 hours at room temperature. The solution was poured into 25% sodium bicarbonate (100ml), washed with dichloromethane (2x50ml) and acidified with 5N hydrochloric acid. The precipitate obtained was separated by filtration and recrystallised from acetonitrile/water to give the title compound (0.15g) mp 258-262°C.

Example 62

4-(2-Naphthyl)salicylic acid

(a) tert-Butyl lithium (100ml,1.5M in pentane) was added over 20 minutes to a solution of 2-bromonaphthalene (13.8g) in tetrahydrofuran (300ml) at -78°C under nitrogen. The mixture was stirred for a further 90 minutes at -78°C after the addition was complete and then transferred into a solution of triisopropylborate (37.6g) in tetrahydrofuran (50ml) at -78°C. The reaction mixture was stirred for 30 minutes at -78°C after the transfer

was complete, quenched with 2N hydrochloric acid, diluted with ethyl acetate (300ml), the organic phase washed with water (2x200ml), dried ($MgSO_4$) and solvent removed. Recrystallisation of the residue from ethyl acetate/hexane gave 2-naphthylboronic acid (6.6g) mp 243-246°C as a colourless solid.

(b) Palladium acetate (0.134g) and 1,1'-bis(diphenylphosphino)ferrocene (0.443g) were warmed together in dimethylformamide (15ml) at 50°C for 30 minutes. To the orange solution 2-naphthylboronic acid (3.76g), 3-bromoanisole (3.74g) and triethylamine (4.0ml) were added and the mixture heated at 100°C for 4 hours. The cooled mixture was filtered through a celite pad the filtrate diluted with ethyl acetate (200ml) and washed with water (5x100ml) dried ($MgSO_4$) and solvent removed. The residue was chromatographed (hexane-50%hexane/dichloromethane eluant) the appropriate fractions combined, solvent removed and the residue recrystallised from a small volume of ethanol to give 3-(2-naphthyl)anisole (2.21g), mp 78-79°C.

(c) 2-Methoxy-4-(2-naphthyl)benzoic acid (0.78g) isolated as a pale buff solid mp 126-128°C was prepared according to the method of Example 59(c) from 3-(2-naphthyl)anisole (1.17g).

(d) The title compound (0.3g), isolated as a colourless solid mp 253-254°C after recrystallisation from ethanol, was prepared according to the method of Example 59(d) from 2-methoxy-4-(2-naphthyl)benzoic acid (0.5g)

Example 63

Ethyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate sodium salt

(a) Diethyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate (1.4g) isolated as a pale yellow oil after column chromatography (silica gel, 1:1 hexane dichloromethane), was prepared according to the method of Example 60(a) from 3-(2-naphthyl)anisole (2.3g). δ(DMSO-d_6) 1.26(t,6H), 4.06(m,4H), 7.32(dd,1H), 7.37(m,1H), 7.54-7.59(m,2H), 7.66(dd,1H), 7.81(dd,1H), 7.94-8.06(m,3H) and 8.23(s,1H).

(b) From diethyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate (0.64g) the title compound (0.35g) isolated as a colourless solid, mp 297-299°C after recrystallisation from water, was prepared according to the method of Example 60(b).

Example 64

n-Butyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate sodium salt

(a) Di-n-butyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate (0.85g) isolated as a colourless oil after column chromatography (silica gel, 3:2 hexane/dichloromethane eluant) was prepared according to the method of Example 60(a) from 3-(2-naphthyl)anisole (1.49g) and di-n-butyl chlorophosphate. δ(DMSO-d_6) 0.88(t,6H), 1.32-1.41(m,4H), 1.55-1.63(m,4H), 3.92-4.09(m,4H), 7.31-7.42(m,2H), 7.53-7.60(m,2H), 7.65(dd,1H), 7.81(dd,1H), 7.94-8.07(m,3H) and 8.22(s,1H).

(b) From di-n-butyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate (0.83g) the title compound (0.35g) isolated as a colourless solid mp darkens above 250°C after recrystallisation from water was prepared according to the method of Example 60(b). δ(DMSO-d_6) 0.79(t,3H), 1.19-1.31(m,2H), 1.38-1.48(m,2H), 3.57-3.68(m,2H), 7.16(dd,1H), 7.25(dd,1H), 7.48-7.61(m,3H), 7.85(dd,1H), 7.92-8.07(m,3H) and 8.24(s,1H).

Example 65

Ethyl 2-hydroxy-4-(9-phenanthryl)phenyl phosphonate sodium salt

(a) 9-Phenanthrylboronic acid, a colourless solid, mp >300°C after recrystallisation from ethyl acetate, was prepared from 9-bromophenanthrene according to the method of Example 62(a). δ(DMSO-d_6) 7.60-7.72(m,4H), 7.97(dd,1H), 8.04(s,1H), 8.37-8.41(m,1H), 8.48(s,2H) and 8.78-8.84(m,2H)

(b) To a solution of 3-methoxyphenol (2.48g) and diisopropylethylamine (3.23g) in dichloromethane (40ml) phenyltrifluoromethanesulphonimide (7.14g) was added in one portion. The reaction mixture was stirred at room temperature overnight, washed with water (2x50ml), saturated ammonium chloride (50ml) and saturated sodium chloride (50ml), dried ($MgSO_4$) and solvent removed to give 3-methoxyphenyl trifluoromethanesulphonate (4.3g) as a colourless oil. δ($CDCl_3$) 3.81(s,3H), 7.02-7.11(m,3H) and 7.50(t,1H).

(c) 3-Methoxyphenyl trifluoromethanesulphonate (1.2g) 9-phenanthryl boronic acid (1.33g), lithium chloride (0.46g) and tetrakis(triphenylphosphine)palladium[0] (0.22g) in a mixture of ethanol (22ml), toluene (54ml) and

aqueous sodium carbonate (2M,7ml), were heated together at 95°C for 2 hours. The mixture was filtered through celite, the organic phase separated, dried ($MgSO_4$) and solvent removed. Column chromatography (silica gel, petroleum ether/dichloromethane eluant) gave 3-(9-phenanthryl)anisole 1.01g mp 95-96°C after recrystallisation from ethanol as a colourless oil. $\delta(CDCl_3)$ 3.86(s,3H), 6.94-7.14(m,3H), 7.33-7.74(m,6H), 7.82-7.99(m,2H) and 8.57-8.78(m,2H).

(d) To a solution of 3-(9-phenanthryl)anisole (0.945g) in dichloromethane (10ml) at -78°C, boron tribromide (1.5g) was added. The reaction mixture was stirred at -78°C for 1 hour and at 0°C for 2 hours. After quenching with water the organic phase was washed with water (2x20ml), dried ($MgSO_4$) filtered and solvent removed to give 3-(9-phenanthryl)phenol (0.9g) as a colourless oil.(d) $\delta(CDCl_3)$ 4.97(s,1H), 6.93(dd,1H), 7.00-7.24(m,3H), 7.38(t,1H), 7.50-7.69(m,4H), 7.87-7.95(m,2H), 8.72(d,1H) and 8.77(d,1H).

(e) A solution of 3-(9-phenanthryl)phenol (0.85g), diethyl phosphite (0.48g) and triethylamine (0.353g) in carbon tetrachloride (20ml) was stirred at room temperature overnight. The reaction mixture was washed with 2N hydrochloric acid (1x20ml), 2N sodium hydroxide solution (3x20ml) and water (1x20ml), dried ($MgSO_4$) and solvent removed at reduced pressure to give diethyl 3-(9-phenanthryl)phenyl phosphate (0.91g) as a colourless oil. $\delta(CDCl_3)$ 1.37(t,6H), 4.19-4.31(m,4H), 7.21-7.71(m,9H), 7.89(d,2H), 8.71(d,1H) and 8.78(d,1H).

(f) A solution of diethyl 3-(9-phenanthryl)phenyl phosphonate (0.9g) in tetrahydrofuran (5ml) was added to lithium diisopropylamide (prepared from diisopropylamine (0.40g) and n-butyllithium (2M in hexane, 2ml)) in

tetrahydrofuran (5ml) at -78°C. The reaction mixture was stirred for 20 minutes at -78°C and for 1 hour at 0°C during which a colourless precipitate formed. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with diethyl ether (50ml), washed with water (2x30ml), the organic phase dried ($MgSO_4$) filtered and solvent removed at reduced pressure. Column chromatography (silica gel, 5% ethyl acetate/hexane-25% ethyl acetate/hexane) and recrystallisation from ethyl acetate/hexane gave diethyl 2-hydroxy-4-(9-phenanthryl)phenyl phosphonate (0.5g) mp 143-146°C as a colourless solid. δ(DMSO-d_6) 1.30(t,6H), 4.01-4.19(m,4H), 7.04-7.16(m,2H), 7.59-7.90(m,7H), 8.07(dd,1H), 8.88(d,1H) and 8.98(d,1H).

(g) The title compound (0.055g) isolated as a pale buff solid, mp >300°C after recrystallisation from water, was prepared from diethyl 2-hydroxy-4-(9-phenanthryl)-phosphonate (0.67g) according to the method of Example 60(b). δ(DMSO-d_6) 1.08(t,3H), 3.66(m,2H), 6.77(dd,1H), 6.86(dt,1H) 7.48(dd,1H), 7.57-7.77(m,5H), 7.92(d,1H), 8.04(dd,1H), 8.87(d,1H) and 8.93(d,1H).

Example 66

Ethyl 4-(1-naphthyl)salicylate

A solution of 4-(1-naphthyl)salicylic acid (3.29g) in absolute ethanol (50ml) was saturated with hydrogen chloride and refluxed for 5 hours. Solvent was removed at reduced pressure, the residual oil dissolved in diethyl ether, washed with water (2x50ml), saturated sodium hydrogen carbonate (50ml) and saturated ammonium chloride (50ml), dried ($MgSO_4$) and solvent removed at reduced pressure. The oil obtained was recrystallised from hexane and then from aqueous ethanol to give the title compound

(0.35g) mp 64-66°C as a colourless solid.

Example 67

6-(1-Naphthyl)-3-[5-(2-pivaloyloxymethyl)tetrazolyl]-pyridin-2(1H)-one

A mixture of 6-(1-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one (1.39g), pivaloyloxymethyl chloride (0.75g) sodium bicarbonate (0.42g) and sodium iodide (0.05g) were combined in dimethylformamide (5ml) and warmed at 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate (50ml), washed with water (6x50ml), dried ($MgSO_4$) and solvent removed. The residue was column chromatographed (silica gel, dichloromethane-5% dichloromethane/ethanol eluant) to give the title compound (0.6g) m.p. 171-172°C after recrystallisation from propan-2-ol.

Example 68

Ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate

From ethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate (0.69g) the title compound (0.23g) m.p. 197-198°C after recrystallisation from ethyl acetate/hexane was prepared according to the method of Example 67.

Example 69

Pharmaceutical compositions for oral administration are prepared by combining the following :

	% w/w		
6-(9-phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one	0.5	3.0	7.14
2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

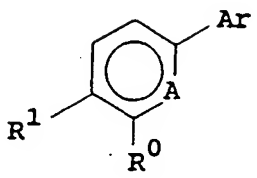
The formulations are then filled into individual soft gelatin capsules.

Example 70

A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 17 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

1. A compound of the formula (1) :



(1)

or a pharmaceutically acceptable salt thereof, wherein :

A is N or CH

R^0 is OH or a bioprecursor thereof,

R^1 is A^0CO_2H, $P(X)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is a single bond, CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkyl-C_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

X is O or S and

Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy, 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy, 3-phenanthryl, 9-phenanthryl, 2-quinolinyl, 4-quinolinyl, 3-thianaphthenyl or 2-benzofuranyl.

2. A compound according to claim 1 wherein R^0 is OH or OR^7 in which R^7 is C_{1-4}alkyl, arylC_{1-4}alkyl, C_{1-4}alkanoyl, arylsulphonyl or C_{1-4}alkylsulphonyl.

3. A compound according to claim 1 or 2 wherein R^1 is A^0CO_2H or $A^0CO_2R^8$ in which R^8 is an ester-forming group.

4. A compound according to claim 1 or 2 wherein R^1 is $P(X)(OH)(OR^2)$ or $P(X)(OR^2)_2$.

5. A compound according to claim 1 or 2 wherein R^1 is 5-tetrazolyl, SO_2H or SO_3H.

6. A compound according to claim 1 wherein R^1 and R^0 are linked together such that R^1-R^0 is A^1CO_2 in which A^1 is CH_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$.

7. A compound according to claim 1 wherein R^1 and R^0 are linked together such that R^1-R^0 is A^2OCH_2O in which A^2 is $P(X)(OR^2)$ or $CR^3(CO_2R^8)$ and R^8 is an ester-forming group.

8. A compound according to any one of claims 1 to 7 wherein Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy.

9. A compound according to any one of claims 1 to 7 wherein Ar is 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy.

10. A compound according to any one of claims 1 to 7 wherein Ar is 3-phenanthryl or 9-phenanthryl.

11. A compound according to any one of claims 1 to 7 wherein Ar is 2-quinolinyl or 4-quinolinyl.

12. A compound according to any one of claims 1 to 7 wherein Ar is 2-benzofuranyl or 3-thianaphthenyl.

13. A compound according to claim 1 which is :

6-(2-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(1-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(2-benzofuranyl)-3-(5-tetrazolyl)-pyridin-2(1H)-one,

6-(9-phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(3-phenanthryl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-(2-quinolinyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-[1-(4-methoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

3-carboxy-6-(2-naphthyl)pyridin-2(1H)-one,

3-carboxy-6-(1-naphthyl)pyridin-2(1H)-one,

ethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-butyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-hexyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

phenyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-butyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-hexyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

ethyl 2-hydroxy-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate,

2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-propionic acid,

2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

2-propoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

ethyl 2-hydroxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphonic acid,

2-oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

ethyl 2-oxo-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

7-aza-6-(1-naphthyl)benzofuran-2-one,

4-ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)-pyridine,

ethyl [6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonothioate,

3-methoxycarbonyl-6-(2-naphthyl)pyridin-2(1H)-one,

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate,

3-(5-tetrazolyl)-6-[2-(1-propyloxy)naphthyl]pyridin-2(1H)-one,

6-[2-(1-pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

2-hydroxyethyl 2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylate,

2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-1,3-dioxolane-2-carboxylic acid,

n-butyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

3-(5-tetrazolyl)-6-(3-thianaphthenyl)pyridin-2(1H)-one,

6-(4-quinolinyl)-3-(5-(tetrazolyl)pyridin-2(1H)-one,

6-[1-(4-hydroxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

2-methoxyethyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

n-propyl [6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

n-propyl [6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]-phosphonate,

2-hydroxy-2-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

ethyl 2-methoxy-2-[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2-ethoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

3-carboxy-6-(9-phenanthryl)pyridin-2(1H)-one,

6-[1-(4-propoxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

ethyl 2-hydroxy-[6-(9-phenanthryl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2-oxo-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

2-hydroxy-2-[6(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]-acetic acid,

n-butyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]sulphinic acid,

ethyl 2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetate,

2,2-difluoro-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]acetic acid,

4-(1-naphthyl)salicylic acid,

ethyl 2-hydroxy-4-(1-naphthyl)phenyl phosphonate,

5-[2-hydroxy-4-(1-naphthyl)phenyl]tetrazole,

4-(2-naphthyl)salicylic acid,

ethyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate,

n-butyl 2-hydroxy-4-(2-naphthyl)phenyl phosphonate,

ethyl 2-hydroxy-4-(9-phenanthryl)phenyl phosphonate,

ethyl 4-(1-naphthyl)salicylate,

6-(1-naphthyl)-3-[5-(2-pivaloyloxymethyl)tetrazolyl]-pyridin-2(1H)-one, or

ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate, or

a pharmaceutically acceptable salt thereof.

14. A compound according to any one of claims 1 to 13 for use as a medicament.

15. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 13 and a pharmaceutically acceptable carrier.

16. A process for preparing a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof which process comprises :

a) for compounds wherein A is N and R^1 is CO_2H or CO_2R^8 in which R^8 is an ester-forming group, reacting a compound of the formula (2) :

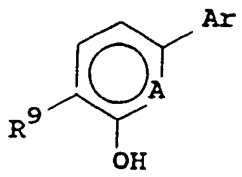
$$ArCOCH=CHY \qquad (2)$$

with a compound of the formula (3) :

$$R^8O_2CCH_2CONH_2 \qquad (3)$$

wherein Y is a displaceable group and Ar is as defined in claim 1 and R^8 is as hereinbefore defined and thereafter optionally converting CO_2R^8 into CO_2H; or

b) for compounds wherein R^1 is CO_2H, hydrolysing a compound of the formula (4) :



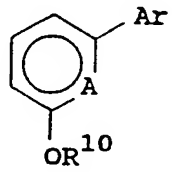
(4)

wherein A is N or CH and R^9 is cyano and Ar is as hereinbefore defined; or

c) for compounds wherein R^1 is A^0CO_2H or $A^0CO_2R^8$ and :

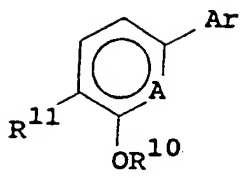
i) A^0 is a single bond,

reacting in the presence of a strong base a compound of the formula (5) :



(5)

wherein R^{10} is methyl, and Ar and A are as hereinbefore defined with carbon dioxide to form a compound of the formula (6) :



(6)

wherein R^{11} is carboxy and Ar, A and R^{10} are as hereinbefore defined and thereafter optionally reacting with R^8OH, wherein R^8 is as hereinbefore defined,

ii) A^0 is $CR^3(OR^4)$,

reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with a compound of the formula (7) :

$$R^3COCO_2R^8 \qquad (7)$$

wherein R^3 is as defined in claim 1 and R^8 is as hereinbefore defined to form a compound of the formula (6) wherein R^{11} is $CR^3(OH)CO_2R^8$ and R^3, R^8, R^{10}, A and Ar are as hereinbefore defined and thereafter optionally reacting with a C_{1-3}alkylating agent to form the corresponding compound wherein R^{11} is $CR^3(OC_{1-3}alkyl)CO_2R^8$,

iii) A^0 is CO,

reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with a compound of the formula (8) :

$$R^8O_2CCO_2R^8 \qquad (8)$$

wherein R^8 is as hereinbefore defined to form a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined,

iv) A^0 is $CH(OH)$,
reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a reducing agent to form the corresponding compound wherein R^{11} is $CH(OH)CO_2R^8$, or

v) A^0 is CH_2,
reacting a compound of the formula (6) wherein R^{11} is $COCO_2H$ or $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a suitable reducing agent to form the corresponding compound wherein R^{11} is CH_2CO_2H, or

vi) A^0 is $C(OR^5)(OR^6)$,
reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a C_{1-3}alcohol, 1,2-ethanediol or 1,3-propanediol to
form the corresponding compound wherein R^{11} is $C(OR^5)(OR^6)CO_2R^8$,

vii) A^0 is CF_2,
reacting a compound of the formula (6) wherein R^{11} is $COCO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CF_2CO_2R^8$, or

viii) A^0 is CHF,
reacting a compound of the formula (6) wherein R^{11} is $CH(OH)CO_2R^8$ and R^8, R^{10}, A and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CHFCO_2R^8$,

and thereafter optionally :

° converting the group OR^{10} into OH

° converting the group $A^0CO_2R^8$ into A^0CO_2H; or

d) for compounds wherein R^1 is CH_2CO_2H, converting a compound of the formula (4) wherein R^9 is acetyl and Ar and A are as hereinbefore defined into the corresponding compound wherein R^9 is CH_2CO_2H; or

e) for compounds wherein R^1 is $P(O)(OH)(OR^2)$, hydrolysing a compound of the formula (4) wherein R^9 is $P(O)(OR^2)_2$ and R^2 is as defined in claim 1 and A and Ar are as hereinbefore defined; or

f) for compounds wherein R^1 is $P(S)(OH)(OR^2)$, converting a compound of the formula (4) wherein R^9 is $P(O)(NHR^{12})(OR^2)$ and R^{12} is phenyl or C_{1-4}alkyl into the corresponding compound wherein R^9 is $P(S)(OH)(OR^2)$; or

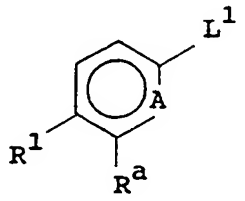
g) for compounds where R^1 is SO_3H, reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with sulphuryl chloride or a chemical equivalent thereof and optionally converting the group OR^{10} into OH; or

h) for compounds wherein R^1 is SO_2H, reacting in the presence of a strong base a compound of the formula (5) as hereinbefore defined with sulphur dioxide and optionally converting the group OR^{10} into OH; or

i) for compounds wherein R^1 is 5-tetrazolyl, reacting a compound of the formula (4) wherein R^9 is cyano or a compound of the formula (6) wherein R^{11} is

cyano with an azide salt; or

j) for compounds wherein R^1 is as defined for compounds of the formula (1) reacting in the presence of a palladium catalyst a compound of the formula (9):



(9)

wherein R^1 and A are as hereinbefore defined and R^a is R^0 or OR^{10} as hereinbefore defined and L^1 is a leaving group with a compound of the formula (10):

$$ArB(OH)_2 \qquad (10)$$

wherein Ar is as hereinbefore defined and then, if necessary, converting the group OR^{10} into OH,

and optionally thereafter :

- forming a bioprecursor of R^0 and/or R^1
- forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/00789

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC C 07 D 401/04, 405/04, Int.Cl.5: 405/14, 401/14, 213/80, C 07 F 9/58, C 07 D 491/04, A 61 K 31/44, C 07 D 213/64, C 07 F 9/6571, C 07 D 213/80, 405/04, C 07 C 65/05, C 07 F 9/40, C 07 D 213/71

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 401/00 C 07 D 403/00 C 07 D 405/00 C 07 D 407/00 C 07 D 213/00 C 07 D 257/00 A 61 K 31/00, C 07 D 491/00, C 07 F 9/00, C 07 C 65/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0347027 (SMITH KLINE) 20 December 1989 ---	1,14
A	CHEMICAL ABSTRACTS, vol. 96, no. 15, 1982, page 680, abstract no. 122589b, (Columbus, Ohio, US), A. ESSAWY et al.: "Synthesis and some reactions of 3-cyano-4-phenyl-6-[1-(2-methoxynaphthalenyl)]-2-pyridone", & REV. ROUM. CHIM. 1981, 26(8), 1141-8, see 1,2-dihydro-6-(2-methoxy-1-naphthalenyl)-2-oxo-4-phenyl-3-pyridinecarboxylic acid, RN=81188-58-1 ---	1
A	EP,A,0308020 (MERCK & CO.) 22 March 1989, see claim 1 ---	1,14
A	US,A,3703582 (MERCK & CO.) 21 November 1972, see column 45, line 71 -----	1,14

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14-08-1991	- 3. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100789 SA 47479

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 20/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0347027	20-12-89	AU-A- 3309689	26-10-89
		JP-A- 1311067	15-12-89
EP-A- 0308020	22-03-89	JP-A- 1128969	22-05-89
US-A- 3703582	21-11-72	BE-A- 752457	24-12-70
		CA-A- 957377	05-11-74
		DE-A- 2031230	07-01-71
		FR-A,B 2053021	16-04-71
		GB-A- 1271767	26-04-72
		NL-A- 7008619	29-12-70
		SE-B- 374367	03-03-75